

Locally Advanced Primary and Recurrent Rectal Cancer

**Surgical experience after Multimodality Treatment
at the Norwegian Radium Hospital**

by
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Thesis

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***To Else
&
Magnus, Marianne, Arne, Espen, Mette***

TABLE OF CONTENTS

TABLE OF CONTENTS.....	7
1. PREFACE.....	9
ACKNOWLEDGEMENTS.....	9
ABBREVIATIONS.....	10
LIST OF PAPERS	13
I.....	13
II.....	13
III.....	13
IV.....	13
V.....	13
2. GENERAL INTRODUCTION	15
EPIDEMIOLOGY OF RECTAL CANCER.....	15
HISTORY OF RECTAL CANCER SURGERY.....	15
<i>Early history of rectal cancer surgery</i>	15
<i>Palliative surgery</i>	16
<i>Local recurrence rate</i>	16
<i>History of TME</i>	16
<i>Surgical history of locally advanced rectal cancer (LARC)</i>	16
The problem	16
En bloc resection	17
En bloc resection after neo-adjuvant treatment.....	18
<i>Surgical treatment of local recurrence after rectal cancer surgery</i>	18
<i>Lateral pelvic side-wall nodal involvement</i>	19
<i>Cylindrical APE for low rectal cancer</i>	19
HISTORY OF ADJUVANT AND NEO-ADJUVANT THERAPY IN LARC.....	20
<i>Early development in neo-adjuvant treatment</i>	20
<i>Candidates for neo-adjuvant therapy</i>	20
<i>Multidisciplinary teams</i>	20
<i>Postoperative CRT</i>	20
<i>Preoperative RT in mobile rectal cancer</i>	21
<i>Preoperative RT/ CRT in LARC</i>	22
<i>Chemotherapy in LARC</i>	23
<i>Induction chemotherapy</i>	23
<i>RT/ CRT in recurrent rectal cancer</i>	23
<i>Intraoperative radiotherapy (IORT)</i>	24
TREATMENT OF METASTATIC DISEASE	24
<i>Liver metastases</i>	25
<i>Lung metastases</i>	25
<i>Ovarian metastases</i>	26
<i>Peritoneal carcinomatosis</i>	26
STAGING OF RECTAL CANCER.....	26
PROGNOSTIC FACTORS IN LARC AND LRRC	27
THE NORWEGIAN DEVELOPMENT OF RECTAL CANCER TREATMENT	28
<i>Treatment at the Norwegian Radium Hospital Cancer Center</i>	28
TME	28
LARC	29
Late recurrences in LARC.....	29
Recurrent rectal cancer.....	30
SURGICAL TRAINING AND OUTCOME.....	30
3. AIMS OF THE STUDY	33
4. MATERIAL AND METHODS	35
PATIENT AND STUDY DESIGN	35
FOLLOW-UP	36

DATA VALIDATION	36
METHODOLOGICAL CONSIDERATION	36
STATISTICAL METHODS	37
5. SUMMARY OF PAPERS	39
PAPER I	39
PAPER II	40
PAPER III	41
PAPER IV	42
PAPER V	43
6. GENERAL DISCUSSION	45
HETEROGENEITY IN CLASSIFICATION OF LARC/ LRRC	45
ONCOLOGICAL OUTCOME	47
<i>Local recurrence</i>	48
<i>Survival</i>	49
EXTENDED RESECTIONS IN LARC AND LRRC	50
COMPLICATIONS	52
MULTIMODAL TREATMENT IN THE ELDERLY	53
MRI IN STAGE T4A LARC	54
7. CONCLUSIONS AND FUTURE PERSPECTIVES	59
8. REFERENCES	61
9. PAPERS I–V	81

1. PREFACE

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Abbreviations

APR	Abdominoperineal resection
CEA	Carcinoembryonic antigen
CI	95% confidence interval
CMI	Circumferential margin involvement
CRM	Circumferential resection margin
CRT	Chemoradiotherapy
CT	Computed tomography
DNR	the Norwegian Radium Hospital, Rikshospitalet
ECOG	Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group (ECOG)
EORTC	European Organisation for Research and Treatment of Cancer
ETME	Extended total mesorectal excision
FFDC	The Fédération Francophone de Cancérologie Digestive
FLIRI	Combination of irinotecan/ fluorouracil/ leucovorin
FLOX	Combination of oxaliplatin/ fluorouracil/ leucovorin, nordic scedule
FOLFOX	Combination of oxaliplatin/ fluorouracil/ leucovorin (bolus and long time)
FU	Fluoro-uracil
HIPEC	Hyperterm intraperitoneal chemotherapy
IORT	Intraoperative radiation therapy
LAR	Low anterior resection
LARC	Locally advanced rectal cancer
LPLD	Lateral pelvic lymphadenectomy
LR	Local recurrence
LRRC	Locally recurrent rectal cancer
MDT	The Colorectal Cancer Multidisciplinary Team
MERCURY	Magnetic Resonance Imaging and Rectal Cancer European Equivalence
mr	staging after MRI evaluation
MRI	Magnetic resonance imaging
p	staging after histopathologic evaluation
PET	positron emission tomography
R0	microscopically free circumferential and distal margins
R1	microscopically involved margins
R2	macroscopic residual cancer in the pelvis or no resection
RT	Radiotherapy
TNM	Tumour Node Metastasis
TME	Total mesorectal excision
TRG	Tumour regression grade
y	any staging following neo-adjuvant therapy
yp	any staging following histopathologic evaluation after neo-adjuvant therapy

Definitions

Adjuvant therapy (Andre and Schmiegel 2005)	Postoperative treatment aimed at reducing rates of local recurrence and metastases after a complete surgical resection (R0 and R1)
Circumferential resection margin	The shortest distance from the tumour or mesorectal tumour deposits to the lateral resection margin
Curative intention	No evidence of distant metastasis before or during surgery, and macroscopic complete resection of the tumour R0 and R1)
Curative resection (Nelson et al. 2001)	A complete resection, without evidence of macro- or microscopic residual tumour, leading to a R0 classification.
Incidence rate	Number of new cases of disease in a definite population over a given time period divided by total persons at risk during that period
Locally advanced rectal cancer	The definition has changed over time from a clinical definition to a definition based upon MRI evaluation. See pages 17 and 45.
Multivisceral resection	Removal of any organ or structure to which primary tumour was adherent
Neo-adjuvant therapy (Andre and Schmiegel 2005)	Preoperative oncological treatment to enable a curative resection in advanced tumours as well as improving local and distant control through reduction in tumour size.
Palliative therapy (Andre and Schmiegel 2005)	Aimed at symptom reduction and/ or prolonged survival in patients not curable with surgery
Progression-free survival	The length of time from randomisation/ inclusion to date of progressive or recurrent disease

TNM classifications 6th edition (Sobin L.H. and Wittekind 2002)

T- Primay tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through muscularis propria into subserosa or into non-peritonealized pericolic or perirectal tissue
T4	Tumour directly invades other organs or structures and/ or perforates visceral peritoneum*

N- Regional lymph nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis**
N1	Metastasis in 1 to 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes***

M- Distant metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Comments to TNM 6th edition (Sobin L.H. and Wittekind 2002):

- * : Tumour that is adherent to another organ is classified T4; however, if no tumour is present in the adhesion microscopically, the classification would be pT3.
- ** : If the examined lymph nodes are negative, but the number ordinarily resected is not met, pN0 is used.
- ***: TNM 6th edition classifies a nodule in the mesorectum with form and contour of lymph node as a regional lymph node metastasis. If the nodule has irregular contour, it should be classified in the pT category and also coded as venous invasion.

Comments to TNM 5th edition (Sobin L.H. and Wittekind 1997):

In the TNM 5th edition a nodule greater than 3 mm in diameter in perirectal or pericolic tissue without histological evidence of a residual lymph node in the nodule is classified as regional lymph node metastasis. However, a tumour nodule up to 3 mm in diameter is classified in the T category as discontinuous extension, i.e., T3.

pN0: Histological examinations of a regional lymphadenectomy specimen will ordinary include 12 or more lymph nodes.

List of papers

I

Larsen SG, Wiig JN, Giercksky K-E. Hydronephrosis as prognostic factor in pelvic recurrence from rectal and colon carcinomas. *Am J Surg* 2005; 190:55-60 (Larsen et al. 2005).

II

Larsen SG, Wiig JN, Tretlie S, Giercksky K-E: Surgery and preoperative irradiation for locally advanced or recurrent rectal cancer in patients over 75 years of age. *ColoRectalDis* 2006; 8: 177-185 (Larsen et al. 2006).

III

Larsen SG, Wiig JN, Dueland S, Giercksky K-E. Prognostic factors after preoperative irradiation and surgery in locally advanced rectal cancer. *EJSO* 2008, 34(4): 410-417 (Larsen et al. 2008).

IV

Wiig JN, Larsen SG, Dueland S, Giercksky K-E. Preoperative irradiation and surgery for local recurrence of rectal and rectosigmoid cancer. Prognostic factors with regard to survival and further local recurrence. *Colorectal Dis* 2008, 10(1): 48-57 (Wiig et al. 2008).

V

Larsen SG, Wiig JN, Emblemvaag HL, Grøholt KK, Hole KH, Bentzen A, Dueland S, Vethrus T, Giercksky K-E. Extended TME in locally advanced rectal cancer (T4a) and the clinical role of MRI evaluated neo-adjuvant downstaging (Larsen S.G. et al. 2008). In press. "Postprint"; doi: 10.1111/j.1463-1318.2008.01649.x

2. GENERAL INTRODUCTION

Epidemiology of rectal cancer

Colorectal cancer is one of the most common cancers in Norway. The incidence rate is highest in North America, Australia/ New Zealand and Western Europe. In 2006 1686 new tumours of colon, rectum and anus were diagnosed in Norway in males and 1767 in females. 569 men and 435 women were diagnosed this year with adenocarcinomas less than 20 cm from anal verge¹. Cancer incidence has been monitored in Norway since 1953. Data (2006) from the Cancer registry of Norway shows an age-adjusted incidence rate (per 100 000) of 14.0 for males and 9.3 for women (Cancer Registry of Norway 2007). Over the last 50 years there has been an increase in incidence but the rate of annual increase has slowed recently.

Colorectal tumours may be divided into proximal and distal tumours in relation to the splenic flexure due to different biological and clinical characteristics identified in the lesions of proximal and distal colon (Bufill 1990). Distal tumours are in the majority of cases aneuploid, rarely display microsatellite instability, but contain a higher frequency of allelic losses and mutations in the p53 gene and KRAS mutation in 20-30% of patients (Lothe et al. 1993).

At the end of 2006, 6.8% of the inhabitants in Norway were 75 years of age or older. The elderly will represent an increasingly larger proportion of the population of Norway in the next quarter of a century, predominantly as a result of prolonged life expectancy. In 2030 it is expected that 20% will be 65 years or older. Rectal cancers diagnosed in Norway 1997-2001 have a total 5-year relative survival rate of 58.5% in males and 60.5% in women (Larønningen 2008). This is more than a 50% improvement during the last 30 years.

History of rectal cancer surgery

Early history of rectal cancer surgery

The first surgeon to practice rectal resection for cancer was probably Faget in 1739 (Goligher 1984). Later, the procedure of abdominoperineal resection (APR) was developed by Ernest Miles in 1908, based on pathological studies. He claimed that the direct and lymphatic spread of rectal cancer occurred in three directions; upwards, laterally and downwards and concluded it necessary to remove the entire rectum, anal canal, sphincters, some of the levator and ischiorectal fat to prevent recurrences (Miles 1908). The relevance of lateral and downward spread was challenged by several authors in the 1930-s (Goligher et al. 1951; Gordon-Watson and Dukes 1930). In 1940, the low anterior resection (LAR) with hand-sewn colorectal anastomosis was introduced by Dixon (Pack and Livingstone 1940) after recognition that it was not always necessary to remove the entire rectum. Increasingly use of staplers and modified technique enabled more sphincter saving

¹ Data for rectal cancer 0-16 cm from anal verge have not been supplied by the Cancer Registry of Norway before 2007.

procedures to be performed in the late 1970-s, with acceptable functional results (Goligher et al. 1979;Heald 1980).

Palliative surgery

Excision of the primary tumour of the colon and rectum for palliative purposes was seldom used before 1940 despite its use in the 1910-s by Mayo and Miles (Modlin and Walker 1949). The overall resectability rate for rectal cancer was only 47% at St. Mark's Hospital (1928 – 1932) including two percent palliative resections. Twenty-five years later the resectability rate had risen to 93%, including 16% palliative resections (Bussey 1969).

Local recurrence rate

Several reports have demonstrated a high frequency of local recurrence after potentially curative rectal resections. An extensive review of the problem was presented by Abulafi in 1994 (Abulafi and Williams 1994). Local recurrence rates in patients without distant metastasis, operated before the era in total mesorectal excision (TME) vary between 10% and 32% in materials with different stages (Hurst et al. 1982;Stipa et al. 1991;Vandertoll and Beahrs 1965). The essential aim of curative resections is to obtain free circumferential resection margins. The recurrence rate was high if microscopic positive resection margins was left after surgery (Quirke et al. 1986;Wibe et al. 2002b). Circumferential margin involvement (CMI) has also been shown to adversely affect long-term survival (Wibe et al. 2002b);Kuo, 2007 423 /id}.

History of TME

In 1978 Richard J. Heald questioned the traditional procedures and developed the TME (Heald et al. 1986). Under direct vision, he performed a complete excision of the envelope of lymphovascular fatty tissue surrounding the rectum. After the introduction of surgical stapling for the anorectal muscle tube, a precise surgical dissection from above increased. The result was the lowest rate of local recurrence yet published and improved outcome of mobile rectal cancer. Local recurrence rates were reduced to 6% at 5-years and 8% at 10-years and improved survival with up to 80% disease free survival (Heald et al. 1998;Wibe et al. 2002b). Moran adapted the linear stapler machine to perform double stapling technique (Moran et al. 1992). TME was widely accepted as the gold standard in rectal cancer surgery that future adjuvant strategies will have to challenge (Heald et al. 1998;Wibe et al. 2002b). The technique was adapted early in Norway and Sweden, and improved results on a national basis have later been published from different countries (Arbman et al. 1996;Enker et al. 1995;Leo et al. 1996;Wibe et al. 2002b).

Surgical history of locally advanced rectal cancer (LARC)

The problem

In unselected patient series of rectal cancer, 10%-20% have a tumour which is primary locally non-resectable on account of extensive growth and fixation to adjacent organs (Pahlman et al. 1985). The median survival of patients who could

not undergo resection was less than one year in the 1950-s and the patients seldom lived for more than two years (Astler and Collier 1954;Bjerkeseet and Dahl 1980).

LARC/ non-resectable rectal cancer are still heterogenous groups. There is no uniform definition of resectability and the tumour can vary from tethered or marginally resectable cancer to a fixed cancer with direct invasion of adjacent organs and structures. The fixation can be due to inflammatory processes as well as tumour invasion. In addition, the assessment of resectability is often made after clinical and radiological investigations before or at the time of surgery. The most important factor for local control and survival is the question of whether residual disease remains in the pelvis after surgery or not. Most recently, three risk groups (low, intermediate and high) have been introduced based upon magnetic resonance imaging (MRI) (Salerno et al. 2006b).

En bloc resection

In the era before neo-adjuvant treatment, LARC in some cases was thought to be removable but not curative since achievement of free margin was unlikely. Wide *en bloc* resections of adjacent organs were described as the treatment of choice, but failure rates remained high with 5-year survival rates of only 19-33% after surgery alone. The Mayo Clinic reviewed their surgical experience with 65 patients with LARC without signs of distant metastasis in the period 1956-84. Extended pelvic resections and *en bloc* resection of all involved organs with curative intent were performed. There were no perioperative deaths, and overall 5-year survival rate was 52% with a local recurrence rate at 5-year of 18% (Devine and Dozois 1992;Orkin et al. 1989). However, these patients represented only 1.5% of the patients undergoing surgery for rectal cancer during the same time period.

Experience with 101 extended resections in the M.D. Anderson Cancer Center showed a 5-year survival rate of 54% if negative tumour margins were achieved and a mean survival of 11 months if the margins were positive (Curley et al. 1992b).

In Heidelberg between 1982 and 1998, multivisceral resections were performed in 201 of 2,712 patients (median 64 years of age). Postoperative complications occurred in 33% and 7.5% died within three months. Potentially curative resections were possible in 130 (65%) but histological tumour infiltration was shown in 44% of patients with intention of curative resection. After curative resection, without positive resection margins, the local recurrence rate was 11% and the overall 5-year survival rate was 51% (Lehnert et al. 2002). A study from 1971 to 1981 showed a local recurrence rate of approximately 30% after *en bloc* resection of the contact patch to the rectal tumour when the adjacent organ had histologically proven carcinomatous invasion (Heslov and Frost 1988).

Decrease in the local recurrence rate has been documented when *en bloc* resection was performed as opposed to when dissection between the neoplasm and adherent structures were done (18% versus 69%). The overall survival was increased (Gall et al. 1987;Hunter et al. 1987). An in-continuity posterior vaginectomy was advocated when the rectovaginal septum was involved (Ruo et al. 2003).

En bloc resection after neo-adjuvant treatment

If aggressive preoperative chemoradiotherapy (CRT) was followed by extensive surgical resection and intraoperative radiation therapy (IORT), the Mayo Clinic managed to increase the 5-year survival rate to 42% in LARC and to 18% in recurrent disease (Farouk et al. 1997). Reasonable benefit and acceptable morbidity and mortality must be provided if an operative procedure should be accepted of value. The quality of life should be considered as well, especially if the treatment requires for instance a cystectomy with ileal conduit as well as a colostomy (Devine and Dozois 1992). However, in our institution we have previously shown that total pelvic exenteration is compatible with a good quality of life (Guren et al. 2001). Postoperative mortality at 30 days was 4% (n = 2) and in-hospital 13% (n = 6) whereas 18 patients had major complications and 12 were reoperated. The higher postoperative morbidity and mortality indicated the need for well-defined indications for this procedure and the necessity for thorough preoperative staging (Wiig et al. 2002a).

Surgical treatment of local recurrence after rectal cancer surgery

Recurrence may cause a reduced quality of life with pelvic pain, bleeding, stenosis or fistulas to vagina, bowel or bladder. The local recurrence rate after operation for mobile rectal cancer has dramatically dropped to 5-10% after the introduction of total mesorectal excision (TME) (Heald and Ryall 1986; Wibe et al. 2002b). Autopsy studies from the time before the TME-era, demonstrated that as many as 25%-50% of these patients had cancer limited to the pelvis at the time of death (Cohen and Minsky 1990; Welch and Donaldson 1978). Thus it seems worthwhile to invest considerable effort in the treatment of local recurrence. In such cases the surgery for locally recurrent disease can be palliative due to distant metastases.

Others have claimed that hydronephrosis secondary to locally recurrent rectal cancer (LRRC) represents a local manifestation of disseminated disease with almost no probability of long-term survival or cure and that adequate surgical result can not be achieved (Lev-Chelouche et al. 2001; Lopez et al. 1987).

Over time, our contraindications for surgery have been reduced and now include: Tumour infiltrating the first sacral vertebra, extension into sacral foramen, involvement of the fifth lumbar or first sacral nerve or major involvement of the common or external iliac vein. However, in LRRC we have been to some extent reluctant to perform this surgery after CRT in patients older than 80-82 years.

The diagnosis and treatment of LRRC are among the greatest challenges for the colo-rectal teams. The crude 5-year survival in patients with LRRC treated with preoperative irradiation and surgery is about 25% (Gunderson et al. 1997; Wiig et al. 2000). Without treatment, patients with LRRC have a median survival of 3 – 6 months (Welch and Donaldson 1978).

A 5-year survival rate for local recurrence of only 5% has been reported after radiotherapy (RT) alone (Wong et al. 1998). Gunderson and Wallace found that surgery combined with preoperative irradiation significantly increased survival

(Gunderson et al. 1996;Wallace, III et al. 1995) compared to surgery alone (Bozzetti et al. 1997;Schiessel et al. 1986).

Major experience with the ultra radical in-continuity sacrectomy together with an APR or pelvic exenteration in recurrent disease has been reported from Memorial Sloan-Kettering Cancer Center (Wanebo and Marcove 1981), University of Virginia (Wanebo et al. 1987), University of Colorado (Pearlman et al. 1987) and Mayo Clinic (Magrini et al. 1996) with excellent pain control presumably related to surgically induced hypesthesia as well as tumour control. The actuarial 5-year survival rate was 25% and median survival was 36 months. Selected patients with pelvic recurrence of rectal cancer may be retrieved by and returned to functional life with the composite abdominosacral resection (Wanebo et al. 1987).

Lateral pelvic side-wall nodal involvement

The significance of lateral pelvic side-wall nodes remains controversial (Koch et al. 2005). Even in extended TME operations these nodes are often left *in situ*. In Japan the nodes are considered to be important regarding survival and local recurrence and are routinely removed in middle and low cancers. In Europe and North America surgical removal of these nodes has been uncommon, and obviously involved nodes are often treated with RT or CRT (Suzuki et al. 1995;Yano and Moran 2008). The main indication for extended lymphadenectomy is low rectal cancer (Sugihara et al. 2006;Yano and Moran 2008). Ueno and colleagues demonstrated that the rate of lateral nodal metastases among T3/4 low rectal cancers below 8 cm was 17% (Ueno et al. 2005;Yano and Moran 2008). Morbidity and mortality rates vary with the degree and extent of surgery. Affection of bladder function and anal sphincter after these lateral pelvic lymphadenectomy (LPLD) operations are not uncommon and sexual dysfunction has been reported in 70-80% of the patients (Hojo et al. 1989;Yano and Moran 2008). Moriya has developed and refined nerve-sparing techniques to achieve acceptable urinary function (Moriya et al. 1995;Yano and Moran 2008). Still there is a controversy as to whether involved pelvic nodes represent systemic disease, M1, as suggested by the current (sixth edition) of the TNM classification (Sobin L.H. and Wittekind 2002) or localised disease, N3, as outlined in the Japanese guidelines (Japanese Society for Cancer of the Colon and Rectum 2006). In a Japanese study the 5-year survival rate in patients with positive lateral nodes was 45%, whereas that of patients with Stage III disease with negative lateral nodes was 71% (Sugihara et al. 2006). The techniques of LPLD may vary from “node picking” to extended *en bloc* resections after CRT.

Cylindrical APE for low rectal cancer

Among 136 consecutive operations for rectal tumours below 5 cm, Heald found the oncological results after LAR superior to those after APR with 4% versus 47% local recurrence rate (Heald et al. 1997). The perineal wound after APR was proposed to be a prerequisite for local recurrence (LR). Surgeons in Stockholm have described a more radical approach to APR surgery (Holm et al. 2007), not unlike the original Miles operation (Miles 1908). Here an extended perineal dissection was performed with the patient in prone position. The cylindrical technique is recently found to

remove more tissue around the tumour that leads to a reduction in CMI and intraoperative perforations (West et al. 2008).

History of adjuvant and neo-adjuvant therapy in LARC

Early development in neo-adjuvant treatment

Ionising radiation has been used in cancer treatment for more than 100 years, and is, after surgery, the second most important single treatment modality for cure of cancer. The rationale for combining surgery with RT is based on the observation that, although RT rarely fails at the periphery of a tumour, surgery is often limited at the same periphery by the need to preserve vital structures adjacent to the lesion. Preoperative RT was therefore introduced to try to sterilize peripherally located disease and to induce tumour shrinkage, thereby allowing radical surgery.

Candidates for neo-adjuvant therapy

To avoid local recurrences both awareness of the importance of lateral clearance and the appropriate use of RT have reduced the risk. To handle circumferential margin involvement, patients with potentially affected margins (Marijnen et al. 2005; Wibe et al. 2002b), and other poor prognostic factors like peritumoral lymphovascular invasion (Gunderson et al. 2004), low-lying tumours (Marr et al. 2005), performance of APR (Holm et al. 2007; Salerno et al. 2006a; West et al. 2008) and pathologic T4 stage (Chan et al. 2005; Kuo et al. 2007) need to be identified preoperatively. Accordingly, neo-adjuvant therapy and the relevant modification of the surgical procedure can then be planned.

Multidisciplinary teams

The Colorectal Cancer Multidisciplinary Team (MDT) is composed of specialist surgeons, oncologists, radiologists, histopathologists and specialist nurses. The MDT should implement an agreed treatment strategy in rectal cancer patients based on nationally accepted guidelines with the aim of standardising and improving outcomes. Studies show that MDT discussion of MRI and implementation of a preoperative treatment strategy results in significantly reduced positive CRM in rectal cancer patients (Burton et al. 2006).

Postoperative CRT

Two large prospective randomized trials conducted in the 1980-s demonstrated an improved outcome with the use of postoperative chemotherapy and external beam RT (Douglass, Jr. et al. 1986; Krook et al. 1991). Following these publications the National Institutes of Health made a consensus statement that postoperative 5-FU (fluoro-uracil) combined with RT was the standard of care for T3, T4, or N1 stage rectal cancer (NIH consensus conference 1990). In a study from our institution a 1-month postoperative combination regimen of RT (46 Gy) and chemotherapy (5-FU)

improved treatment results in patients with Dukes' B and C rectal cancer versus surgery alone, both in recurrence rate and survival (Tveit et al. 1997).

Preoperative RT in mobile rectal cancer

Preoperative RT for rectal cancer was established at Memorial Hospital in the late 1950-s, suggesting a significant therapeutic benefit but identical survival (Stearns, Jr. et al. 1974). Over a 25-year span (1957-82) the Veterans Administration Surgical Oncology Group (VASOG) performed prospective, randomized studies also regarding preoperative RT with 31.5 Gy and rectal cancer (Higgins et al. 1986). They found increased survival after APR in the RT versus the control group and reduced incidence of positive lymph nodes in the resected specimens after preoperative RT (35% versus 41%). The survival benefit could not be reproduced in a second study.

The first scandinavian trial conducted in preoperative RT, was a multicenter trial in western Norway (Dahl et al. 1990). In the period 1976 – 1985 more than 300 patients were randomized between surgery and preoperative RT with 1.75 Gy x 18 with surgery after 2 to 3 weeks. The time to recurrence was doubled after RT (27 versus 13 months) but no survival benefit could be demonstrated.

In Sweden, the primary aim was to decrease the local failure rates by sterilizing tumour cells. Since there was no need for either decrease in size or stage of the primary tumour, short course schedules with immediate surgery were explored (Glimelius 2006; Willett et al. 2007). In the Uppsala study, preoperative, short course, high-dose RT (5.1Gy x 5) decreased the local recurrence rate relative to postoperative long course RT (2 Gy x 30 with a delay after 40 Gy). There was no sign of increased late morbidity after a follow-up of 5 to 10 years (Frykholm et al. 1993).

The Swedish Rectal Cancer Trial (5.1Gy x 5) showed improved 5-year survival (58% versus 48%). They also documented a reduced recurrence rate (11% versus 27%) in the surgery alone group (Swedish rectal cancer trial 1997). Both studies are from the era before TME surgery.

The benefit of this RT regimen in combination with TME surgery was also suggested in a Dutch trial where 1861 patients with TNM stage I to IV were randomised to either short course RT and TME surgery or TME surgery alone (Kapiteijn et al. 2001). The combination treatment reduced local recurrence rate after two years from 8% to 2% ($p<0.001$) but this difference did not improve overall survival (81.8% versus 82%). There was a persisting effect of preoperative short course RT on local control in those patients with clinically resectable rectal cancer (6% versus 11% 5-year recurrence rate). There was no effect on overall survival (Peeters et al. 2007). However, more long-term bowel dysfunction with increase in faecal incontinence was found in irradiated patients than in patients who underwent TME alone (62% versus 39%), and the sexual function in both men and women was decreased. These results led to future strategies in order to select patients with high risk of local failure (Peeters et al. 2005).

Preoperative RT/ CRT in LARC

Only randomized trials can provide strong evidence of a positive cost-benefit ratio of combined approaches. In the German so called CAO/ ARO/ AIO study they compared preoperative conventionally fractionated RT and concurrent fluorouracil chemotherapy with nearly the same treatment given postoperatively (addition of boost 5.4 Gy) in TME operated LARC (Sauer et al. 2004). A high 5-year survival rate but no difference between pre- and postoperative treatment was found (76% and 74%). However, the proportion of T4 tumours was less than 1% and all patients with clinical T3 and T4 or node-positive disease were included. Preoperative CRT reduced the local recurrence rate (6% versus 13%) and acute toxic effects (grade 3 and 4) were also lower in the preoperative group (27% versus 40%).

Results of different phase II trials in the United States have addressed results of CRT (Crane et al. 2003b; Guillem et al. 2005; Minsky et al. 1994; Onaitis et al. 2001). At Duke University, after neo-adjuvant long course CRT with 5-FU and cisplatin they found positive lymph node status to predict increased local recurrence and decreased survival (Onaitis et al. 2001). A report from Memorial Sloan-Kettering Cancer Center showed a prolonged long-term outcome in patients achieving more than 95% response to preoperative CRT (Guillem et al. 2005). After 5-FU based CRT at M. D. Anderson Cancer Center the clinical response to the treatment contributed to 49% sphincter-preserving surgery and 47% clinical complete response rate (Crane et al. 2003b). In this study, clinical complete response was defined as cases with either no residual or only microscopic residual disease in the resected specimen.

The rate of complete responses between 10% and 20% led to the hypothesis that neo-adjuvant treatment could improve local control and sphincter saving procedures (Ortholan et al. 2006). This was strongly supported in retrospective studies (Crane et al. 2003b). The EORTC 22921 trial by Bosset et al demonstrated that chemotherapy (5-FU/ Leucovorin), regardless of administration before or after surgery, gave a significant benefit with respect to local control, and that addition of chemotherapy to preoperative RT had no effect on survival (Bosset et al. 2006).

The FFCD 9203 trial randomizing RT with or without 5-FU/ Leucovorin, in T3-4N0-2M0 rectal cancer, significantly improved local control with increase of pT0 (11.4% versus 3.6%) and decreased local recurrence rate (8.1% versus 16.5%) (Gerard et al. 2006). On the other hand there was a moderate increase in acute toxicity (14.6% versus 2.7%).

Long-term results from a Polish trial showed that neo-adjuvant long course CRT did not increase survival, local control or late toxicity compared with short course RT alone in clinical stage T3 or T4 rectal cancer. The 5 Gy x 5 group was operated within 7 days while the long course group was given 1.8 Gy x 28 (totally 50.4 Gy) and TME was performed after 4-6 weeks. Survival of LARC has increased by multimodal therapy to more than 50% (Vauthey et al. 1999).

Recently, a new treatment modality with short course RT and postponed surgery has been advocated from the Uppsala group (Radu et al. 2008). The regimen was well tolerated in high age and considering the very advanced local stage, the schedule had substantial anti-tumour activity and resulted in radical surgery in a high proportion of patients (locally R0 in 65%, 32/46 patients).

Chemotherapy in LARC

A National Cancer Institute Consensus Conference in 1990 recommended the use of postoperative CRT for patients with stage II and III rectal cancer as standard treatment. The drugs of choice were 5-fluorouracil (5-FU)-based chemotherapy.

The rationale for preoperative CRT has been the potential advantage of eliminating distant micro metastases at an early stage, enhance radiosensitivity due to better oxygenation of the tissue, reduce toxicity from the RT and increase the preservation of the anal sphincter. The prize has been increased rates of complications. In a Canadian study, the addition of 5-FU based chemotherapy to RT as neo-adjuvant treatment (3 cycles of 5-FU 370 mg/m²/day) and leucovorin (200 mg/m²/day) at 1,4 and 9 weeks) increased the rates of pelvic sepsis (anastomotic leak and pelvic abscesses) from 5% to 24% (Buie et al. 2005).

Induction chemotherapy

More recently neo-adjuvant chemotherapy prior to CRT and surgery has been used in patients with LARC. In a study from Royal Marsden hospital a combination of protracted venous infusion of 5-FU for 12 weeks with mitomycin C (MMC) bolus every 6 weeks before CRT, 5-FU during long course RT and postoperatively chemotherapy as well, were given (Chau et al. 2006).

Induction chemotherapy can possibly also increase the proportion of complete pathological downstaging after CRT, usually with new drugs (Chau et al. 2006; O'Neill et al. 2007). Up to 25% of patients have been registered as having pathological complete responses after CRT, and some authors advocate avoiding surgery especially if surgery would involve a permanent colostomy (Habr-Gama et al. 2004). At the Royal Marsden Hospital and Pelican Cancer Foundation a pilot study has commenced investigating a non-operative approach to complete responders (O'Neill et al. 2007).

RT/ CRT in recurrent rectal cancer

Local recurrence of rectal cancer after RT and adequate surgery is fortunately rare. Even if recurrence developed, it can be possible to re-irradiate and to add intra-operative radiotherapy (IORT) or brachytherapy. There are only few retrospective studies with the value of reirradiation. From Uppsala reirradiation with 30 Gy over three weeks after recurrence of rectal cancers given short course RT were evaluated. The treatment was well tolerated but no long term survivors were reported (Glimelius 2003). From the Mayo clinic, experience from 51 previously irradiated patients with recurrence was reported (Haddock et al. 2001). After IORT and additional external RT, overall survival was 48% after two years and 12% after five years. However, a trend versus improved local control was registered. Peripheral neuropathy was the main IORT-related toxicity.

An American study on 103 reirradiated patients demonstrated longer median survival (44 months versus 14 months) and increased 5-year survival (22% versus 15%) in the 34 patients that could be treated with surgical salvage after reirradiation with 15 – 49 Gy, median 35 Gy (Mohiuddin et al. 2002).

There is still no general established practice for reirradiation in LRRC but high doses of reirradiation can be delivered with acceptable risk without prohibitive long-term side effects (Mohiuddin et al. 2002). Different patient series vary in both fractionation and total dose. In February 2008 we changed our policy at DNR and introduced hyperfractionated treatment with 1.5 Gy twice a day (at least 6 hours between doses) to a dose of 42-45Gy to increase surgical salvage and long-term survival of the patients (Mohiuddin et al. 2002). Capecitabine (Xeloda) 825 mg/ m² are given the same days as RT. If recurrence is diagnosed less than 12 months after primary RT, palliative RT with 2 Gy x 10-15 might be given.

Intraoperative radiotherapy (IORT)

The use of IORT in aggressive multimodality treatment at The Mayo Clinic was discussed earlier (Farouk et al. 1997). This allows for the delivery of high biologically and locally effective doses of radiation while dose-limiting structures are displaced. The biological effectiveness of single-dose IORT has been suggested to be two to three times the equivalent dose in fractionated external beam RT (Gunderson et al. 1988). In that way the addition of 10 Gy to 50 Gy external RT is equivalent to 70-80 Gy. Until late in the 1990-s IORT was given to selected patients in our department. IORT was terminated as we were not able to identify any definite effect of the procedure (Wiig et al. 2002b). Later a study from MSKCC suggested that there is a need for randomised studies on the effect of IORT on R0 resection (Dresen et al. 2008; Shoup et al. 2002). Recently a Dutch group has also found that IORT cannot compensate for a R1 resection (Dresen et al. 2008).

Treatment of metastatic disease

Fluorouracil plus folinic acid had an established role in the treatment of advanced colorectal cancer and was the standard combination for most patients until late the 1990-s with response rates of about 30%. In studies where oxaliplatin was combined with different infused FU regimens and folinic acid as first-line treatment of metastatic disease, the response rates were doubled and progression-free survival prolonged (de Gramont A. et al. 2000; Levi et al. 1997; Sorbye et al. 2004). This was even the case when oxaliplatin was combined with the more feasible bolus schedule Nordic FLOX (Sorbye et al. 2004). 5-FU/calciumfolinate combined with oxaliplatin or irinotecan is usually given as first line treatment for patients below 75 years, and most of them respond. Median survival is close to two years (Sorbye et al. 2008).

The progress in molecular and tumour biology has produced a great number of new “targeted” drugs like the monoclonal antibodies bevacizumab (Avastin®) targeting vascular endothelial growth factor (VEGF) and cetuximab (Erbix®) targeting

epidermal growth factor receptor (EGFR). Bevacizumab combined with an irinotecan regimen is an alternative first line treatment (Sorbye et al. 2008).

Efficacy analyses in the CRYSTAL trial have shown improved progression free survival and curative surgery rate when adding cetuximab to irinotecan/ FLV (FOLFIRI) in first line treatment of metastatic colorectal cancer. The patients with wild-type KRAS mutation status (KRAS oncogen) showed an additional treatment effect with cetuximab in addition to FOLFOX (Van Cutsem et al. 2008).

The new CAIRO2 study from the Dutch Colorectal Study Group presented at ASCO 2008 showed that addition of the second antibody cetuximab to capecitabine (Xeloda®), oxaliplatin and bevacizumab resulted in significantly decreased median progression free survival (9.8 versus 10.7 months) (Punt et al. 2008).

Liver metastases

Up to 30% of patients treated for colorectal cancer have synchronous hepatic metastases (Penna and Nordlinger 2002). General indications for resection were less than four lesions even when bilobar, no extrahepatic disease, and expected resection margins of at least 10 mm (Ekberg et al. 1986). Resections must preserve a sufficient remnant of tissue for normal liver function (Hellinger MD and Santiago CA 2006). The possibilities of ex vivo resections have increased the indications in later years (Raab et al. 2000). Patients with single, easily accessible lesions can have the resection concomitant with the rectal surgery. Usually the liver resections are performed in later procedures. The 5-year survival rate for curative resections approaches 35% (Fong et al. 1999), but relapse is common and occurs in 75% of patients (Nordlinger et al. 1996). Portier et al have demonstrated that adjuvant intravenous systemic chemotherapy provided disease-free survival benefit for patients with resected liver metastases from colorectal cancer (Portier et al. 2006). After a median follow-up of 87 months, the 5-year disease-free survival rate was 33% in the chemotherapy group and 26% in the control group. There was a trend towards increased overall survival (51% vs. 41%).

Neo-adjuvant chemotherapy and surgery can reduce the risk of relapse as Nordlinger showed in a new EORTC Intergroup trial (40983) where perioperative FOLFOX4 chemotherapy was compatible with major surgery and increased the progression-free survival (Nordlinger et al. 2008). Chemotherapy has also been used in downstaging hepatic metastases to make the liver resectable (Bismuth et al. 1996; Meric et al. 2000).

Lung metastases

Lung metastases occur in 10 to 20% of colorectal cancer patients. Patients are candidates for surgical intervention when single lesions occur. Palliative procedures do not improve survival (Ike et al. 2002). Surgery can be performed as formal lung resections (pneumonectomy, lobectomy) or as un-anatomical resections (wedge resections) often with a laser technology. A markedly lower success rate for more than two lesions have been found (Ike et al. 2002; Penna and Nordlinger 2002). The

morbidity is much lower than after liver resections (2% versus 12%). 5-year overall survival in these patients varies between 14 and 78%, 30% after re-resections (Hellinger MD and Santiago CA 2006).

Even combinations of lung- and liver resections can in some cases be performed with acceptable results, 25 to 30% 5-year survival but with a high rate of re-recurrence (75%) (Lehnert et al. 1999).

Ovarian metastases

Bilateral involvement is observed in 50% to 70% of patients with ovarian metastasis. Because of the possibility of occult disease, the treatment of isolated ovarian metastases is bilateral salpingo-oophorectomy. The median survival was less than 18 months (Sielezneff et al. 1997), but in one study the median survival in resectable disease was 48 months (Morrow and Enker 1984).

Peritoneal carcinomatosis

Peritoneal carcinomatosis is found in 10-15% of patients synchronous with the primary colorectal tumour, and in as much as 40-70% of recurrent disease (Minsky et al. 1988). Half of the patients with synchronous metastasis were free of systemic metastases (Jayne et al. 2002). The treatment is shifting from minimalistic approach to very active management (Sugarbaker 2003). Maximal cytoreductive surgery and hyperterm intraperitoneal chemotherapy (HIPEC) is the most proactive treatment. The Amsterdam group randomized patients with histologically proven carcinomatosis between chemotherapy and palliative surgery to cytoreduction and HIPEC (Verwaal et al. 2003) and the median survival was better (22 versus 13 months). The median survival exceeds 2 years, and 5-year survival rates are as high as 20-30%, similar to surgery for liver metastasis (Moran et al. 2006). The treatment is resource demanding and in our own published experience after HIPEC was introduced in 2003 in 23 patients with carcinomatosis, the median operation time exceeds 9 hours and there is no mortality within three months postoperatively (Larsen S.G. et al. 2006). After perfusion with oxaliplatin and irinotecan at 43° C and systemic 5-FU, the mortality rate in one study was 4% with a complication rate of 66%. The most common complication was digestive fistula (24%), lung infection (16%) and haematological toxicity (11%).

Staging of rectal cancer

Alternative preoperative staging tools include digital rectal examination (Nicholls et al. 1982), endorectal ultrasonography (US) (Mackay et al. 2003), computed tomography (CT) (Beets-Tan et al. 2000; Brown et al. 2004), magnetic resonance imaging (MRI) (Beets-Tan et al. 2000; Brown et al. 2004) and positron emission tomography (PET), often as functional imaging with 18F-2-deoxy-D-glucose as FDG-PET (Denecke et al. 2005). Even though PET might be superior to CT and MRI in predicting response to preoperative multimodal treatment, MRI is superior to evaluate the circumferential

resection margin, depth of extramural tumour and the nodal status (Beets-Tan et al. 2005; MERCURY Study Group 2006; MERCURY Study Group 2007). In future studies a proper MRI examination should be required for an adequate pretreatment staging.

Prognostic factors in LARC and LRRC

Uninvolved CRM has been discussed as the most important prognostic factor for survival and recurrence in resectable rectal cancer (page 16). A number of studies have reported RT to decrease the recurrence rate in LARC (Kapiteijn et al. 2001) and also increased survival rate after R0 resection (49% versus 23%) (Eriksen et al. 2006). The various regimens of RT/ CRT regarding local recurrence and survival are discussed on pages 19-24. Except for a single European trial, definite improvement in survival has not been demonstrated with preoperative RT alone and the survival was low compared to other studies (Swedish rectal cancer trial 1997).

The prognostic values of venous and neural invasion were focused in a study exploring the effect of preoperative RT. Both factors predicted significantly reduced actuarial survival in node-negative tumours (Horn et al. 1990). Venous invasion was found to be a strong independent predictor of metastasis, whereas neural invasion had a strong association with local recurrences (Horn et al. 1991).

Prognosis in LARC after neo-adjuvant treatment is also related to the T-stage and the presence or absent of nodal involvement (Myerson et al. 1995; Onaitis et al. 2001; Theodoropoulos et al. 2002). Coco found both pT- and pN-stage to be correlated with the incidence of metastases and survival (Coco 2006). Wibe observed that in decreasing circumferential margins there was an exponential increase in the rates of local recurrence, metastasis and death (Wibe et al. 2002b).

The optimal timing of surgery after 3 Gy x 13 RT was analyzed in the Lyon trial where 6-8 weeks interval between end of irradiation and surgery was associated with better clinical tumour response and higher pathologic downstaging in T-stage (26% versus 10%) than after 0-2 weeks (Francois et al. 1999).

Sugihara and colleagues reported that uninvolved lateral nodes are the strongest predictor of both survival and local control in patients with primary rectal cancer (Sugihara et al. 2006). After multivisceral resections in LARC without RT intraoperative blood loss, age 65 years or older and stage were independent prognostic factors (Lehnert et al. 2002).

In a PET-study a significant survival benefit was found in patients with low fluorodeoxyglucose uptake after preoperative RT in LARC (Nakagawa et al. 2008).

After oncological treatment of LRRC survival was positively correlated with ECOG performance status (Oken et al. 1982), absence of extrapelvic metastases, long interval from primary surgery to RT of the recurrence and absence of hydronephrosis (Wong et al. 1998). R0 resection and absence of vascular invasion were the only factors to predict improved disease-free - / disease-specific survival and local control

after treatment of LRRC with RT, surgery and IORT in a study from Memorial Sloan-Kettering Cancer Center (Shoup et al. 2002).

After salvage surgery poor prognosis has been reported in patients with recurrence diameter > 3 cm and with tumour fixation in two areas (Lopez-Kostner et al. 2001). In an earlier study from London, the radical nature of the operation, absence of pain, obstruction or sepsis and a diameter less than 5 cm were related to longer survival (Gagliardi et al. 1995b). Carcino-embryonic antigen (CEA) response to normal values after surgery was found to have increased survival.

The Norwegian development of rectal cancer treatment

The Norwegian surgical community addressed the problems with high local recurrences after curatively intended resections early in the 1990-s. National results of 28% local recurrences after rectal cancer resections in 1986 to 1988 (Norstein and Landmark 1997) were in sharp contrast to reports from Heald with 5% and Enker with 7% 5-year recurrence rates (Enker et al. 1995; MacFarlane et al. 1993).

The Norwegian Rectal Cancer Registry enabled the monitoring of outcome of rectal cancer treatment for single hospitals. Early experience from Ullevål Hospital showed doubling of the anastomotic failure rate (16% versus 8%) after introduction of TME (Carlsen et al. 1998). All TME patients with leaks required re-operations compared to 25% of non-TME patients. A defunctioning stoma reduced the problems with leakage. In the period from 1993 – 1999 more than 3000 patients were included in the database, and the rate of RT given was only 10% (Wibe et al. 2006). There has been a gradual increase from 5% of the patients receiving pre- and postoperative RT in 1994 to 23% in 2001, and in the same period the cumulative 5-year local recurrence rate decreased from 16% to 11% (Hansen et al. 2007).

In 1996 combined chemotherapy and long course preoperative RT (2 Gy x 25) was recommended on a national level for patients with fixed, primarily ir-resectable rectal cancer (Bjerkset et al. 1996). From 1999, additional national guidelines recommended postoperative CRT following intraoperative perforation or tumour within 2 mm of the CRM in patients under 75 years of age. The indication for neo-adjuvant treatment in Norway has been changed from 2007 to involve tumour and also metastatic lymph nodes ≤ 3 mm from the mesorectal fascia (Consensus in the Norwegian Gastro Intestinal Cancer Group), and therefore the proportion of neo-adjuvant therapy in Norway will increase further.

Treatment at the Norwegian Radium Hospital Cancer Center

TME

The Norwegian Radium Hospital Cancer Center was among the first to standardise the surgical technique of rectal cancer in Norway under the head, Professor Karl-Erik Giercksky. Senior consultant Johan N. Wiig was one of the Norwegian pioneers in

TME and the technique was adapted in our department after his study period in Basingstoke in 1993.

LARC

Our department has been a tertiary referral cancer centre for multimodal treatment of LARC and LRRC. The numbers of procedures for LARC have increased year by year and during the last five years about 50 patients were treated annually.

In the period from 1990 to 2001, the definition of LARC was based on the clinical evaluation of the tumour (fixed or tethered) in general anaesthesia, and the support of the CT-evaluation regarding infiltration in pelvic structures. Magnetic Resonance Imaging (MRI) has been used routinely since 2002, and the definition of LARC in Norway has been extended from tumour or metastatic lymph nodes ≤ 1 mm of the mesorectal fascia to ≤ 3 mm in 2006.

Pelvic imaging was originally performed with CT but since early 2002 MRI has been routine for all primary cancers and since 2005 for LRRC. Initially the patients were discussed by the oncologists and surgeons. Since 1998 we have had a formal multidisciplinary team of oncologists, surgeons and radiologists to decide whether the patients should be considered for neo-adjuvant therapy. Four weeks after the end of RT another pelvic MRI investigation is performed and a final decision regarding surgery is made. All patients were given long course RT as 2 Gy x 23 to the tumour and threatened lymph nodes followed by 2Gy x 2 as boost against macroscopic tumour, totally 50 Gy (5 weeks) unless this was contraindicated by previous RT or the general condition of the patient.

FLV in a study protocol (LARCS-A) has been given as Nordic schedule from 1996. Chemotherapy concomitant with RT has been routinely given since December 2003 with 3 cycles of 5-FU 400 mg/m² and folinic acid 100 mg during RT.

In the ongoing trial LARC RRP (locally advanced rectal cancer – radiation response prediction) from November 2005 Oxaliplatin and 5-FU (FLOX) are used as induction therapy in two cycles (85 mg/m² day 1, 5-FU 500 mg/m² and folinic acid 60 mg/m² day 1 and 2. Then weekly oxaliplatin 50 mg/m² before RT and concomitant Capecitabine 825mg/m² twice daily during RT (Sunday evening to Friday morning). The latter is an oral tumour-selective fluoropyrimidine, which is converted to FU mainly in tumour tissue.

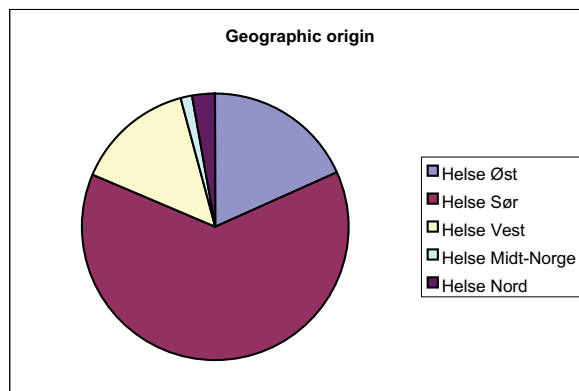
Late recurrences in LARC

Preoperative irradiation may prolong the average time to local recurrences as reported by Coco et al. They found that more than 50% of local relapses occurred more than two years after surgery and even 28% as long as five years after surgery (Coco et al. 2006). In contrast, Guillem found 6% recurrent disease later than five years after surgery and the Colorectal Research Unit in Basingstoke 11% (Guillem et al. 2005; Moore et al. 2005). Accordingly studies with a mean follow up less than two years are difficult to interpret and the follow-up time should be prolonged.

Recurrent rectal cancer

Even though the rate of local recurrence has declined, our department increasingly performs surgery for LRRC. From our health region 152 patients were operated after neo-adjuvant treatment the in last 17 years, whereas 89 patients from the other four health regions were treated (Figure 1).

Figure 1. Recurrent rectal cancer treatment in DNR 1990 – 2007 (n=241).



In the period from 1993 to 2001, 540 patients were the national cohort for treatment of LRRC. 171 patients (31.7%) obtained R0/ R1 resection, whereas 193 patients (35.7%) were given RT but had macroscopic tumour left (R2). 176 patients (32.6%) received no treatment with curative intent or obtained a R2 resection. As much as half the curative resections in Norway (47%) were performed in our department, 29% with R2 after RT and 17% of those without treatment or left with macroscopic tumour without RT (Hansen 2008).

Surgical training and outcome

The general public, the legal profession, patients and relatives expect best practice and have difficulty with the concept of a learning curve for surgical interventions (Moran 2006). The relationship between quality and treatment volume in cancer surgery has been documented in systematic analyses like those from the UK National Health Service Centre for Reviews and Dissemination (Sowdon AJ 1997), from the Institute of Medicine in the US (Hewitt M. 2007) and from The Norwegian Centre for Evaluation of Methods (2008). A study from the Norwegian Colorectal Cancer Project has shown that the rate of local recurrence was higher for hospitals with a low annual caseload than for hospitals with a high treatment volume of 30 or more (local recurrences rate 18% versus 9%). Patients treated in small hospitals also had a shorter 5-year overall survival rate than those treated in large hospitals (58% vs. 64%) (Wibe et al. 2005).

The introduction of TME surgery has demonstrated the effects of surgical training programme on outcome (Martling et al. 2000; Sugihara et al. 2006; Wibe et al. 2006). The Norwegian Rectal Cancer Register was able to demonstrate that the risk of local recurrence of rectal cancer on a national level was significantly reduced (50%) from patients treated in 1994 versus those treated in 1999. Similarly, during 1998, the mean national overall survival was significantly improved, compared to the rate in 1994 (Wibe et al. 2006). The surgical learning curve for complex surgical procedures are shown to be slow (Moran 2006).

3. AIMS OF THE STUDY

TME is widely accepted as the procedure of choice in rectal cancer surgery (Heald et al. 1998; Wibe et al. 2002b). TME has increased long-term survival (Wibe et al. 2002b; Kuo et al. 2007) and reduced local recurrence in general. In cases with microscopic positive resection margins however, the recurrence rate has been reported to be as high as 80% (Quirke et al. 1986). The 5-year survival of LARC has increased after introduction of different multimodality treatments.

The aims of the study were:

- To evaluate the oncological outcome after multimodal treatment for LARC and LRRC, to audit intraoperative and early postoperative complications and to evaluate prognostic factors. The results were examined and prospectively registered in a database. The main hypothesis was that thorough neo-adjuvant treatment and precise surgery could improve the oncological results, with an acceptable rate of complications.

The specific aims were:

- To investigate if the condition of hydronephrosis was a contraindication to surgery in LRRC due to a dismal prognosis (*paper I*).
- To identify and evaluate pre- and perioperative risk factors for morbidity and mortality, and outcome in the elderly, over 75 years of age, after multimodal treatment regimens for LARC or LRRC (*paper II*).
- To examine the results after neo-adjuvant and surgical treatments of patients with clinical LARC in a referral centre and evaluate prognostic factors for survival and recurrence, and parameters for obtaining a free CRM (*paper III*).
- To examine results in a large single centre material of multimodality treatment of LRRC and to evaluate prognostic factors for obtaining free CRM (*paper IV*).
- To evaluate patients with MRI diagnosed organ infiltrating LARC (T4a) and to evaluate MRI before and after neo-adjuvant treatment, the pathological stage of the resected specimen, the R-status and the tumour regression grade (TRG) (*paper V*).

4. MATERIAL AND METHODS

Patient and study design

The Norwegian Radium Hospital Cancer Centre is a tertiary referral cancer centre for multimodal treatment of LARC and LRRC. In the period from September 1990 until April 2007, data from the multimodality treatment of more than 600 patients with rectal cancer were prospectively entered into a database. Senior consultant Johan Wiig started the registration of demographic data and the parameters concerning oncological and surgical treatment in our hospital and the DataEase database was used.

The dataset has given rise to the five studies in this thesis. The study in Paper IV is among the five largest single centre publications in treatment of LRRC so far and the report in Paper V the only to evaluate MRI and histopathology in MRI diagnosed T4 LARC.

The staging workup included endoscopy, biopsy, digital exploration and bimanual palpation in general anaesthesia before and after RT. Patients were classified as rectal cancer if a primary, infiltrating adenocarcinoma of the rectum was bioptically confirmed and located less than 16 cm from the anal verge on stiff proctoscopy. In Papers II and III the diagnosis LARC was based on clinical evaluation in general anaesthesia (fixed or tethered) and evaluation on CT. In Paper V the definition was based on MRI criteria of infiltration into neighbouring organs.

Patients with recurrent tumours are included in Papers I, II and IV. In Paper I confirmed recurrences in the pelvis from rectal and rectosigmoidal tumours (treated with APR, LAR or Hartmann's procedure) were accepted. Thirty-five patients with recurrent disease from primary rectal- and rectosigmoidal cancer were also included in paper II. In Paper IV some primary distal colonic cancers were also included if the recurrence was in the pelvis. Eleven patients had a primary resection of rectosigmoid.

The author has participated in the colorectal treatment program from 1997; performed surgery and follow-up, and participated in the database work. Nearly all patients were operated by two gastroenterological surgeons; Wiig and the author. The data were transformed to a new MedInSight database early in 2007 and much effort have been made in validating the data after converting to a new platform. In the new database, MRI data and histopathological data from 2002-2007 were also retrospectively entered.

About 25% of elderly patients with LARC or LRRC referred to our hospital in the period 1997 – 2000 could not undergo RT/ surgery with curative intent or were advised not to undergo surgery, mainly because of too advanced metastatic disease or severe co-morbidity. These patients would receive palliative irradiation, chemotherapy or best supportive care. Age alone was no absolute contraindication and we have successfully performed combined radiation and surgical treatment in patients elder than 75 years of age.

In Paper IV 17 patients with previous RT/ CRT to the pelvis and 37 patients with known metastases were excluded.

In Paper V 23 of 115 patients with MR diagnosed T4a rectal cancer were excluded; this includes patients who did not receive pelvic RT or where radiation treatment was stopped before 48 Gy (7), not evaluated with MRI both before and after RT (8), only surgically explored (3), where MRI was inadequate (4) or when another pelvic malignancy that could alter the evaluation (1).

In Paper I hydronephrosis was retrospectively evaluated, both at the time before RT and between RT and surgery. Signs of hydronephrosis and hydroureter were, when necessary, further investigated by ultrasonography, urography, CT scans and/ or renography. We used standard radiological definition of hydronephrosis with dilatation of renal pelvis and calyces, and dilatation of ureter down to an obstruction. These 23 patients with hydronephrosis were compared with the 170 patients without.

When performing LAR or Hartmann's procedure the double stapling technique has been routinely performed for more than 10 years. The TME plane is extended (ETME) to perform *en bloc* operation when necessary. Rectal irrigation with sterile water was performed after the first staple was placed below the tumour and before the second was placed. A defunctioning stoma has been increasingly used due to the increased risk of anastomotic leakage after performance of anastomoses in irradiated patients.

Follow-up

All patients attend the out patient clinic in our hospital postoperatively for 5 years with X-ray or CT scan of the chest, CT scan of the abdomen and of the pelvis. The patients in the study were followed every 3 months for 2 years, then every 6 months for the next 3 years. Instances of local recurrence, distant metastasis and death have been continuously registered in the database. Only survival was systematically documented later than five years after performed surgery.

Data validation

Incompletely registered parameters were crosschecked and, if possible, retrieved from other sources. Data regarding death are also crosschecked against the national registry.

Methodological consideration

In large studies the end of an observation period is often registered as one date for the whole group. However, in the study in this thesis the follow-up time has been stated as synonymous with the real observation time for the individual patient.

The TNM system is revised every five years, and the criteria of lymph node metastasis have, for instance, changed from 1997 to 2002. This can lead to stage

migrations and difficulties for ongoing clinical trials. Within the last three versions of the TNM system the classification of tumour deposits has varied enormously, from being ignored in 4th edition, to being defined as an involved lymph node when exceeding 3 mm in 5th edition to being defined by shape in 6th edition. Also venous invasion and micrometastasis have changed the classifications. In the UK and in our hospital we still use the 5th edition (Quirke et al. 2007).

The introduction of R classification in 1978 was a major step forward (Quirke et al. 2007). However, the TNM committee classify R1 to be ≤ 1 mm only if the tumour is in the margin of resection; otherwise the tumour should be classified as R0 (Wittekind et al. 2002). This wider classification of R1 is used in studies from the UK (Adam et al. 1994; Quirke et al. 1986), Norway (Wibe et al. 2002b) and the Netherlands (Nagtegaal et al. 2002), but not for instance from Germany (Rodel et al. 2005).

Statistical methods

Most sets of continuous data in this thesis were of non-normal distribution, and measures of variation were given as median and range values. Mostly we have used the non-parametric tests for differences between groups of quantitative variables (Mann-Whitney test). The association between categorical variables were assessed using chi-square tests (Pearson and linear-by-linear) or Fisher's exact test. p-values of 0.05 or less in a two-sided test were regarded as significant.

In Papers I-IV curves of survival and local recurrence were calculated with the Kaplan-Meier product-limit method and potential prognostic factors were tested for univariate statistical significance with the log rank test. One minus survival plots were used in graphic presentation of local recurrence whereas conventional survival plots were used in presentations of survival.

Some of the potentially interesting risk factors for survival and recurrence from the univariate analysis, with p-values less than 0.10 were entered in a multivariate analysis. This was performed using Cox proportional hazard regression analysis as in Papers II –IV.

Multiple logistic regression analysis was used in the evaluation of possible risk factors associated with achievement of R0 stage in Papers III and IV in order to analyze the influence of each factor on outcome. Generally, the number of covariates in a regression model should not exceed 10-15% of the number of event; decreasing the evaluation of factors or covariates in these minor studies.

In Paper II Fisher's exact probability test for two proportion comparisons was used to evaluate complications regarding different ASA - and age-groups, operation time, preoperative transfusions, tumour level and time between irradiation and surgery. The National Cancer Registry performed survival analysis of the patient group compared with the general population in Norway over 75 years of age, considering year of birth and sex. Relative survival was defined as the probability of the cancer patient surviving a defined short period of time divided by the probability that an age- and gender matched individual will survive the same time period (Ederer et al. 1961).

In paper V the McNemar-Bowker Test is used in evaluation of the dominance of downstaging versus upstaging of both T- and N-stages. All calculations were performed using the latest version of Statistical Package for the Social Sciences® program (SPSS, Chicago, Illinois, USA).

5. SUMMARY OF PAPERS

Paper I

HYDRONEPHROSIS AS PROGNOSTIC FACTOR IN PELVIC RECURRENCE FROM RECTAL AND COLON CARCINOMAS.

Hydronephrosis secondary to pelvic recurrence of colorectal cancer was a condition claimed to represent an absolute contraindication to surgery due to a dismal prognosis (Cheng et al. 2001;Rodriguez-Bigas et al. 1992). The purpose of this study was to examine the condition of hydronephrosis in our recurrent cases.

193 consecutive patients who underwent surgery after RT for pelvic recurrence in rectal or colon cancer from January 1991 until March 2002 were evaluated (121 men and 72 women). Median age was 67 years. Twenty-three had hydronephrosis prior to preoperative irradiation for their relapse.

The frequency of hydronephrosis differed according to the primary surgery; 8.5% after APR, 9.2% after LAR and 18% after Hartmann's procedure. The obstructions were localized just below the common iliac vessels in 9 patients, at the pelvic sidewall in 7 and at the base of the bladder/prostate in 7. The hydronephrosis was severe in 6 patients, moderate in 16 and light in 1. Three patients had bilateral hydronephrosis. The obstruction declined in two patients during RT, two were in need of temporary nephrostomy drainage and two of internal stents during RT.

Multivisceral resections were performed and surgery was more extensive in the patients with hydronephrosis (32 additional organs in the hydronephrosis group versus 148 other pelvic organs in the other 170 patients).

R0 stage resection was obtained in 22% of the patients with hydronephrosis and in 41% without. The median survival time in patients without metastasis (M0) was 27 and 32 months respectively and 5-year survival rates 11 and 25%. R2 resections were the final result in 35% (8 patients) with hydronephrosis and 24% (40 patients) without. Complications were similar in the two groups.

In conclusion, aggressive surgical approach offered patients with pelvic recurrence from rectal and colon cancer the best potential for survival. The presence of hydronephrosis probably indicated a lower chance for complete surgical resection of the recurrence, but local control and improved survival might still be achieved, and about 2/3 of patients might benefit from the operation.

Paper II

SURGERY AND PREOPERATIVE IRRADIATION FOR LOCALLY ADVANCED OR RECURRENT RECTAL CANCER IN PATIENTS OVER 75 YEARS OF AGE.

Reports of multimodal treatment regimens especially focusing on LARC or LRRC in elderly over 75 years of age were missing. The aim was to identify and evaluate pre- and perioperative risk factors for morbidity and mortality and outcome after irradiation/ surgery regimens in elderly patients.

The study was a prospective registration of 86 consecutive patients over 75 years of age undergoing multimodal treatment for LARC (n=51) or LRRC (n=35). The patients underwent surgery from January 1991 to August 2003; 51 men and 35 women, median age 78 years (75 – 85).

Multivisceral resections were needed in 63% of patients and 70% R0 resections were obtained in LARC and 46% in recurrent cancer.

Median operation times were 252 minutes (range 70 - 420) and the time in the intensive care unit 2.3 days (1-15 days). Mean hospitalisation was 14 days (4-65 days) and mean peroperative blood loss 2.0 litre (range 0.5 – 15). In hospital- and 30 days mortality were both 3.5%. Sixty-two postoperative complications occurred in 38 patients, three of them fatal.

5-year survival in R0 patients was 46%; for those with non-metastatic disease (M0) 29% in LARC and 32% in LRRC. The estimated 5-year local recurrence rates were 24% for R0 resections and 54% for R1 resections ($p=0.434$ ns) and 24% and 45% for LARC and LRRC ($p=0.248$ ns) respectively.

Old males had a higher mortality rate the first year after surgery than females with 65% relative survival compared to a matched normal population.

In conclusion, thorough preoperative evaluation and preparation, and judicious surgery are important for achieving potentially curative treatment with acceptable morbidity in patients over 75-year of age with LARC and LRRC. We suggested that these patients should be evaluated and considered for treatment by multidisciplinary teams as younger patients.

Paper III

PROGNOSTIC FACTORS AFTER PREOPERATIVE IRRADIATION AND SURGERY FOR LOCALLY ADVANCED RECTAL CANCER.

The purpose of this study was to examine the results after neo-adjuvant and surgical treatments of patients with clinical LARC in a referral centre and to evaluate prognostic factors for survival and recurrence, and parameters for obtaining a free CRM.

A prospective cohort study of 204 M0 patients underwent surgery in the period 1991-2003. The median age was 66 years, 29% were women and all tumours were located <16 cm from the anal verge.

We performed multivisceral and/or pelvic wall resections in 61% of the patients. R0, R1 and R2 resections were achieved in 74%, 21% and 5% respectively. 5-year survival was 60% for R0 resections, 31% for R1 and 0% for R2. The calculated 5-year recurrence rates were 13% for R0 resections and 24% for R1 resections ($p < 0.035$).

N-stage and histopathological differentiation were the only factors significant for all three endpoints. Downstaging to pT0 was significant for both survival and future development of metastasis. CEA responders had lower recurrence rate than non-responders. R-stage, N-stage, age, type of rectal resection and pelvic wall resection remained significant in Cox multivariate analysis for survival. N-stage, CEA response and pelvic wall resection were prognostic markers for local recurrence. Medium high tumour level and reduced histopathological differentiation are important individual factors that seem to predict increased risk for not obtaining a R0 resection.

The mortality rate within the first month was 2.5% and non-lethal complications appeared in 41% of the patients. Fifty-five re-operations were performed in 41 patients, most often because of bowel or urinary leaks, pelvic abscesses or bowel obstruction.

In conclusion, after preoperative RT and surgery about 50% of the patients with LARC without overt metastases (M0) can be cured.

Paper IV

PREOPERATIVE IRRADIATION AND SURGERY FOR LOCAL RECURRENCE OF RECTAL AND RECTOSIGMOID CANCER. PROGNOSTIC FACTORS WITH REGARD TO SURVIVAL AND FURTHER LOCAL RECURRENCE.

Only three other centres had reported results from experience of more than 100 patients with LRRC (admitted April 2006). The aim of this study was to examine the experience from the Norwegian Radium Hospital and evaluate prognostic factors for obtaining free CRM.

150 patients with local recurrence after rectal/ rectosigmoideal cancer, stage M0, were given preoperative RT/ CRT and data were prospectively recorded.

The median level of recurrence was 1.1 cm anal to the anastomosis in patients with a primary LAR.

The operations were resource demanding with a median duration of 330 minutes, ranging from 60 to 960 minutes. Erythrocyte transfusions were median 3 units (0-37). This did not influence either the survival ($p=0.459$) or the local recurrence ($p=0.962$). The duration of hospitalisation was a median of 18 days (3 – 127 days).

The 30-day mortality was 0.7%, however, non-lethal complications appeared in 46% of the patients with deep pelvic abscesses and late healing of the perineum in a total of 27%. Bowel and urinary leaks developed in 6% and 8%. Re-operations were performed in 32%.

The 5-year survival rate was 27% and the proportion of R0 resections achieved was 44%, R1 resection 38% and R2 resection 17%. The corresponding survival/local recurrence rates were 52% / 27% for R0 stage and 14% / 63% for R1stage. No patients with R2 resection survived more than 4 years.

Normal pretreatment CEA levels significantly increased survival but normalisation by preoperative therapy did not improve prognosis. Survival and local recurrence were also significantly influenced by type of primary operation. Several factors were significant for prediction of R0 resection in univariate analysis, but only CEA and symptoms at recurrence in multivariate analysis.

In conclusion, after preoperative RT/ CRT and surgery a substantial number of R0 resections could be achieved with prolonged survival. Also patients with an R1 resection could benefit from the operation. A substantial number will die without further local recurrence. The surgical achievement was the main prognostic factor followed by CEA level, sex and type of primary operation.

The value of our Norwegian follow-up regimen was questioned because nearly two thirds of the recurrences were diagnosed due to symptoms, in spite of routine follow up programs in the referring hospitals.

Paper V

EXTENDED TME IN LOCALLY ADVANCED RECTAL CANCER (T4a) AND THE CLINICAL ROLE OF MRI EVALUATED NEO-ADJUVANT DOWNSTAGING.

We are neither aware of any published study focusing on MRI stage migration before and after neo-adjuvant therapy in MRI diagnosed T4 patients with LARC, nor any study that evaluates if the repeat MRI after neo-adjuvant treatment improves the surgical achievement.

The aim of this study was to compare the clinical ability of MRI taken before and after neo-adjuvant treatment in LARC to predict the necessary extension of TME (ETME) and the possibility of achieving R0 resection.

92 MRI evaluated T4a primary rectal cancers undergoing elective surgery between 2002 and 2007 were prospectively registered.

MRI identified patients in need of neo-adjuvant treatment and predicted T-downstaging in 10% and N-downstaging in 59%. Seventy-nine percent R0 resections, 18% R1 and 3% R2 were obtained after ETME in 95% of the patients and TME in the rest. Preoperative CRT resulted in more patients obtaining TRG1-3 compared to those receiving RT ($p=0.02$). The pelvic wall was the area of failure in 70% of the R1 resections. Tumour cells outside the mesorectal fascia scattered within fibrosis were obtained in 18 among 33 ypT4 tumours (55%).

MRI cannot discriminate tumour cells within fibrosis. Therefore, if a R0 resection is the goal, we advocate optimal surgery in accordance with the pretreatment MRI. Post-treatment MRI is a poor predictor of final histology and should not be used to guide the extent of surgical resection.

The study has initiated a new approach to histopathological classification of the removed specimen where we introduce a MRI assisted technique for investigating the areas at risk outside the mesorectal fascia in the specimen.

6. GENERAL DISCUSSION

Heterogeneity in classification of LARC/ LRRC

Rectal cancer in general and LARC especially is a heterogeneous disease. The niveau from the anal verge differ from 12 – 16 –20 cm in different studies. Some classify anal and rectosigmoidal cancer together. The diagnostic tools differ; clinical exploration with or without use of general anesthesia, endoscopic procedures with or without use of ultra sound technique and different radiological procedures like CT-, MRI- or PET-scans. Biopsies are often used to confirm the diagnosis in intraluminal tumours whereas fine needle core biopsy (FNCB) or the more sensitive fine needle aspiration cytology (FNAC) often are used outside the intact mucosa (Larsen et al. 1999).

The condition “threatened” mesorectal fascia varies from tumour or suspicious lymph node within 5 mm of the mesorectal fascia to 0 mm. The tumours vary from those respecting the mesorectal fascia to those infiltrating the fascia or even the neighbouring organs. The lymph node statuses differ from N0 disease to advanced distant lymph node metastasis or distant organ affection. Resectability varies from marginally resectable cancer to fixed cancer. Tumours vary from resectable to resectable after multimodality treatment or non-resectable tumours, even after multimodality treatment. Surgery differs from simple rectal resections to MRI evaluated *en bloc* resections after various neo-adjuvant multimodality treatment regimens; RT, CRT, IORT or brachytherapy.

Even the proportion of radical resections can be evaluated differently, as in LRRC, where several authors group the R1 resections together with the R2 resections (Bakx et al. 2004;Bozzetti et al. 1997;Eble et al. 1997;Vermaas et al. 2005), while others group R0/ R1 resections (Wallace, III et al. 1995) or discuss “curative” versus palliative resections (Law and Chu 2000;Lopez-Kostner et al. 2001;Yamada et al. 2001). The frequency of R0 stage varies widely both in LARC and in LRRC due to differences in selection and surgical aggressiveness, illustrated by the wide difference in frequency of sacral resections in recurrent disease (Magrini et al. 1996;Mannaerts et al. 2001;Vermaas et al. 2005). In previous studies of LRRC the frequency of R0 stage varies widely from 12% (Walz et al. 1995) to more than 70% (Yamada et al. 2002).

Some studies have tried to classify LRRC which is usually defined as any recurrence within the true pelvis (Wiig et al. 2005b). The Mayo Clinic used not fixed (F0), fixed at one site (F1), fixed at two sites (F2) or fixed at three or more sites (F3) (Hahnloser et al. 2003). The Cleveland Clinic used a classification after symptoms; asymptomatic, symptomatic without pain or symptomatic with pain (Lopez-Kostner et al. 2001). In Berlin the patterns of recurrence with special emphasis on lateral tumour extension in a CT-based three-dimensional datafile system have been studied (Hocht et al. 2004). In Leeds, MRI evaluation of the tumour recurrence in eight anatomical regions (rectoanal, pelvic bowel, urinary tract, male and female genital tract, pelvic floor, pevic side wall and posterior pelvis) has been used. For each site the appearance was recorded as normal, induction of fibrosis, tumour adherence or tumour invasion (Robinson et al. 2002).

In an earlier study from our department, most recurrences were within one cm of the anastomosis, and no rectal recurrence occurred more than three cm distal to the anastomosis (Wiig et al. 1999). Seventy to 80% of recurrences started perirectally. Based on these observations and the later experience, a new classification has been proposed (Wiig et al. 2007) and modified here (Table 2):

Table 2. Our criteria for LRRC

1. Localized recurrence	1A	Perineal recurrence in the scar after AR
	1B	Tumour in the perineum or anal canal after LAR
	1C	Anastomotic recurrence after LAR
	1D	Recurrence in pelvic lymph nodes
2. Organ infiltrating recurrence	2C	Recurrence affecting central pelvic organs, often anteriorly (vagina, uterus, prostate, bladder, vesicular seminalis)
	2P	Perirectal recurrence infiltrating the pelvic wall, often posteriorly in the area of the anastomosis (sacrum, pelvic nerves S1-3, iliacal vessels, ureter, pelvic floor, m. piriformis)

If the pelvic wall is affected by tumour, the possibility of adequate lateral margins depend on the distance from the pelvic fascia to the neighbouring structures like large nerves or the proximal part of sacrum. Recurrence on the pelvic entrance may affect the common or external iliac vessels or the ureters with need for reconstructive surgery.

Outcome varies with selection of patients, treatment options, volume of performed surgery and tumour stage. The issue is further confused by the fact that some studies exclude patients operated without resections (Shoup et al. 2002). The most important factor for local control and survival however, is whether residual disease remains in the pelvis after surgery or not.

When TME was performed in tumours within the mesorectum more than 1-2 mm lateral resection margin as judged on preoperative MRI and surgical specimen were adequate (Nagtegaal et al. 2002; Wibe et al. 2002a) (Quirke et al. 1986). In T4a rectal cancer (Paper V), and in recurrent disease (Paper IV), this may not be true because we do not know the minimally required circumferential resection margin outside the fascia. Further studies are necessary to enlighten this issue.

Lack of consensus of optimal treatment of LARC is still a problem and, with a few exceptions, we lack large single centre series (Crane and Skibber 2003; Guillem et al. 2005). We have evaluated the oncological outcome after multimodality treatment for LARC and LRRC, to audit intraoperative and early postoperative complications in general and in elderly especially, to evaluate prognostic factors and at last to evaluate MRI in the proportion of LARC infiltrating neighbouring structures.

Oncological outcome

Most of the studies on the results of multimodal treatment of LRRC have included relatively few patients over many years in referral hospitals, suggesting a significant selection (Bakx et al. 2004;Boyle et al. 2005;Bozzetti et al. 1997;Eble et al. 1997;Gunderson et al. 1997;Mannaerts et al. 1999;Wallace, III et al. 1995;Walz et al. 1995;Wong et al. 1998). Only studies from the Mayo Clinic, Memorial Sloan-Kettering Cancer Center and paper IV in this thesis had, in April 2006, included more than 100 patients (Hahnloser et al. 2003;Salo et al. 1999;Shoup et al. 2002) (Table 3).

Table 3. Large single centre patient series in recurrent rectal cancer

Name	Institution	Year	Time	n	Observation time in months	Frequency R	Survival R	Re-recurrence	Mortality/morbidity	comments
Salo (Salo et al. 1999)	MSKCC	1999	1986-95	131 M0	-	R0: 54% R1: 10% R2: 36%	Total:28 mnt R0: 35% R1: 23% R2: 0	-	-	131/194 curative intent
Hahnloser (Hahnloser et al. 2003)*	Mayo Clinic	2003	1981-96	304 M0 resectable 166 pall. op. included	-	R0: 45% R1: 9% R2: 46%	Total: 25%- 31 mnt R0: 37% R1/2: 16%	-	0.3/ 26	304/394 90 found irresectable 138 curative res. 14 exploratory laparotomies included.
Bedrosian (Bedrosian et al. 2006)	MD Anderson	2006	1988-98	85 M0	All: 43	R0: 76% R1: 24% R2: excluded	Total: 36%- R0: 35% R1: 15%	All: 59% Median 11 mnt		134/412 curative intent 49 exploratory laparotomies excluded
Paper IV (Wiig et al. 2008)	DNR	2008	1990-2004	150 M0	All: 23	R0: 44% R1: 38% R2: 17%	Total: 27%- ? mnt R0: 52% R1: 14% R2: 0	R0: 27% R1: 63%	0.7/ 46	150/204 17 RT earlier 37 M1 11 exploratory laparotomies included
Dresen (Dresen et al. 2008)	Catharina Hospital, Eindhoven	2008	1994-2006	147	Survivors: 34	R0: 57% R1: 23% R2: 20%	Total: 31% 28 mnt R0: 48% R1: R2:	All: 50%	4.8/ 59	147/ 184 curative intent

*: Mayo Clinic 90 exploratory laparotomies were excluded.
In the other studies these patients were included (11 in Paper IV)

In Paper III, 16 clinical parameters with regard to their relative prognostic impact on the decisive parameters, survival and local recurrence, were evaluated. Seven of these parameters were known at the time of diagnosis and the rest established after surgery was performed and evaluation of the pathological specimens completed. In univariate analysis 11 of the parameters had a significant impact on survival, 12 on local recurrence and 9 of them on both endpoints.

Local recurrence

In Paper III, the pN0-stage was associated with fewer recurrences than pN2 and was a strong predictor for both endpoints in a multivariate analysis. The importance of lymph node status as a prognostic marker in recurrence was not controversial and historical controls seemed to indicate that nodal metastases were less common in patients undergoing preoperative RT (Graf et al. 1997; Medical Research Council Rectal Cancer Working Party 1996).

R-stage is an important predictor of local recurrence. After R0 resection, we found 5-year local recurrence rate to be lower than usually reported from studies without CRT and in accordance to other studies with shorter observation times (Eriksen et al. 2006; Palmer et al. 2005).

Tumour level was important for local recurrence and resection of part of the pelvic wall of importance for both survival and local recurrence. Tumour levels between 4 and 6cm from the anal verge had higher recurrence rates, probably because of narrow surgical planes deep within the pelvis where the mesorectum became thin, and the technical challenges more demanding. The proportion of sphincter preserving surgery varied in different materials of LARC. The proportion was one third in our study, 22% by Palmer et al, 49% of tumours below 6cm from the anal verge by Crane and 80% by Coco but his material consist of 98% T3 tumours (Coco et al. 2006; Crane et al. 2003b; Palmer et al. 2005).

In both LARC (Paper III) and LRRc (Paper IV) the proportion of patients with elevated CEA level at diagnosis were about 50% (100/191 and 74/150). Half the cases with elevated CEA respond to treatment with normalised values (50/100 and 39/74) after neo-adjuvant treatment. Patients with reduced CEA level in Paper III had lower recurrence rates than those with elevated values. This show CEA to be a strong predictor of recurrence if CEA was elevated as found in Paper IV. However, those with CEA response to treatment in Paper III had lower recurrence rates than non-responders whereas this was not found for re-recurrences in Paper IV. This may be due to small numbers or bias from non-radical resections (R2).

In Paper IV, the local recurrence rates were 27% and 63% for R0 and R1 resections respectively, similar to results from other groups (Boyle et al. 2005), even when adding IORT (Gunderson et al. 1997; Shoup et al. 2002; Vermaas et al. 2005). The prognostic importance of R0 stage has been found in several reports (Boyle et al. 2005; Mannaerts et al. 1999; Shoup et al. 2002) but not in all (Salo et al. 1999). In one paper there was no statistically significant difference between R1 and R2 resections (Gunderson and Sosin 1974).

When hydronephrosis was present (Paper I), locally complete resection was achieved in 22%, half the frequency of R0 resections in the non-hydronephrosis group. Two-thirds had R0/ R1 resections in the hydronephrosis group. In a previous report we found patients with R1 resection doing better than R2 resections (Wiig et al. 2002a). Thus we suggested that both patients with R0 and R1 resections (65%) might benefit from the operation. Correlation between surgical resection stage and prognosis seemed to be in accordance with the suggestion of other authors (Shoup

et al. 2002;Wallace, III et al. 1995). The hydronephrosis was caused by either infiltration of tumour into the ureter or by tumour compression. Resections of ureter and/ or bladder were done in 43% in the hydronephrosis group and decompressed in the rest. Investigation of the specimens in the resection group showed direct invasion into or through the affected ureter in 5, tumour at very close distance in 2 (ostium and vesicle), fibrosis after irradiation in 1, and in 2 patients invasion could not be further evaluated. In contrast, some authors claimed hydronephrosis secondary to LRRC to represent a local manifestation of disseminated disease with almost no probability of long-term survival or cure, and that adequate surgical result can not be achieved (Lev-Chelouche et al. 2001;Lopez et al. 1987). In Roswell Park Cancer Institute, 22 patients who underwent exploration without any resection of tumour were reported. Their results showed low survival rates similar to patients with distant metastasis (Cheng et al. 2001;Rodriguez-Bigas et al. 1992;Wiig et al. 2008).

Survival

In Paper III, we found the ypT-stage to be a strong predictor of survival and the presence of lymph node involvement to adversely affect survival. We found all N-stages to be strong predictors of survival. This corresponds well with results reported after multivisceral resection with 60% and 28% 5-year survival in node negative/ positive patients and 5-year overall survival rates of 47% for N1 and 18% for N2 cases in another study (Chapet et al. 2005;Lehnert et al. 2002). After pelvic exenteration in LARC, 5-year survival rate was higher in previous reports of patients with negative lymph nodes (47%-82%) than in patients with lymph node involvement (25%-55%) (Hida et al. 1998;Ledesma et al. 1981).

The 74% R0 resections obtained in our study was higher than 56% after aggressive multivisceral resection as a single treatment (Lehnert et al. 2002) but lower than 89% following CRT for clinically evaluated T4a tumours (Gohl et al. 2003). A Norwegian multicentre study (Eriksen et al. 2006) reports 51% R0 resections in LARC treated with curative intent without irradiation and 75% in those receiving irradiation. R0 resection was a strong predictor of survival and the survival rate was significantly higher than for R1 and R2 resections. R1 was higher than R2, suggesting that even the achievement of an R1 resection can be of significance to the patients. We analysed factors important for R0 achievement. Tumour with low differentiation histopathologically decreased the odds ratio for obtaining R0 resections 10-fold and the ratio increased with increasing distance from the anal verge. A higher proportion of R0 resections in low T-stages suggested that maximal tumour shrinkage by neo-adjuvant treatment might improve the results.

An APR was associated with decreased survival compared to a LAR in univariate analysis. Similarly, the presence of an annular tumour was suggestive of a more aggressive cancer growth with reduced survival and increased local recurrence. In LRRC, we found longer lagtime after APR than LAR till diagnosis of local recurrence suggesting that the cancer had a better opportunity to more extensively infiltrate the pelvic wall in these cases, as well as more time to develop distant metastases.

In Paper III and IV, we found significantly lower survival rates after surgery when CEA was elevated before irradiation. Our results from CEA monitoring are in

accordance to the observations of Sugarbaker in that persistently low serum CEA titres after irradiation are correlated to disease control, and that CEA response can be used to monitor the effect of RT (Sugarbaker et al. 1976). There has been no previous agreement of the prognostic role of CEA in local recurrence (Gagliardi et al. 1995a; Law and Chu 2000; Maetani et al. 1992; Salo et al. 1999). One could imagine that a normalisation of CEA after RT indicates a radiosensitive cancer only localized in the pelvis and therefore with a better prognosis than patients with persistently elevated CEA. Surprisingly this was not the case in Paper IV. CEA levels above normal therefore seem to indicate a more malignant biology of the cancer. To our knowledge this was the first report showing that there was no correlation between CEA responsiveness to irradiation and outcome in recurrent disease.

The better survival of female gender in recurrent disease was in accordance with some studies (Law and Chu 2000; Lopez-Kostner et al. 2001) but in contrast to others (Gagliardi et al. 1995a; Hahnloser et al. 2003). It is difficult to evaluate whether the difference was due to technical, biological or non-cancer related factors.

Our overall estimated 5-year survival in LRRC (Paper IV) of 27% is better than after surgery alone with less than 10% survival (Bozzetti et al. 1997; Walz et al. 1995) although a small recent study did not find any effect of preoperative RT (Bakx et al. 2004). Our survival rate was similar to reports from groups giving IORT (Hahnloser et al. 2003; Salo et al. 1999). The 52% 5-year survival of R0 in LRRC was about the same as 60% after R0 in LARC (Paper III) but the proportion of patients achieving R0 was much lower (44% versus 74% of patients).

The median survival time in the hydronephrosis group in paper I was 27 months. Aggressive approach to LRRC may lead to 5-year survival rates higher than 50% by selecting patients who could be surgically resected with negative margins and who tolerated extensive surgery (Curley et al. 1992a). Some authors have found the extent of resection to be a significant predictor of improved survival (Shoup et al. 2002; Wallace, III et al. 1995; Wanebo et al. 1992).

Extended resections in LARC and LRRC

The surgical strategy in LARC was based on TME but modified to include tumour-suspect tissue outside the mesorectal plane. To plan such an extended TME (ETME) the surgeon needs as accurate as possible preoperative information about the extensiveness of the malignant process.

In order to obtain radical resections with 61% R0 in Paper II we removed 54 other organs and dissected outside the TME-plane on the pelvic wall in 32 of the 86 patients. Eighteen of 21 R1 resections were among the 63% (n=45) of patients operated with multivisceral resections supporting the view that multivisceral resections might reduce the proportion of R2. Recent reports support the view that locally advanced tumours can be handled more safely with multivisceral resection than with irradiation alone (18).

In order to operate radically in Paper I, cystoprostatectomy was performed five times more often in the hydronephrosis group and hysterectomy twice as often.

Paper III showed that even in combination with preoperative RT/ CRT, extended resections are required to obtain R0 in advanced tumours. The high rate of multivisceral resections clearly illustrated that the whole spectre of pelvic surgery should be available in these patients. By *en bloc* resections, a decrease in local recurrence rate and improved survival can be achieved. This was in accordance with the high recurrence rates reported when dissection is performed between the tumour and adherent structures (69%) (Gall et al. 1987; Hunter et al. 1987). A pelvic wall resection signified a breach by the tumour of the ordinary TME layer, which is clearly demonstrated by the significantly higher number of local recurrences among the 37% of patients with pelvic wall resections.

When pelvic organs had to be resected due to cancer infiltration or narrow margins in Paper IV, this did not seem to worsen the prognosis for survival which was in accordance with previous studies (Hahnloser et al. 2003). As we also had to remove tissue on the pelvic wall in nearly half of the cases, we considered that the majority of patients with involvement of the central pelvic organs would benefit from preoperative irradiation. We have previously shown that total pelvic exenteration can be consistent with a good quality of life (Guren et al. 2001) and believe that such operations should be performed when necessary. It was slightly surprising that patients who had resection of part of the pelvic wall did not have a statistically significantly lower expected survival even though they had a higher frequency of R1 resections.

The experiences with ETME procedures, discussed in this thesis (Paper I to V) are given in Table 4.

Table 4. Multivisceral resections in this thesis

Paper	Inclusion period	Patients	n	RT/ CRT %	IORT %	APR %	LAR %	Hartmann's %	Tumour removal	Expl %	ETME %	Multivisceral resection %	Pelvic wall resection %
III	1/1991 – 12/2003	LARC M0	204	94/6	13	47	32	20	0	1	61	47	37
IV	9/1990 – 1/2004	Rec M0	150	93/7	40	33	10	23	27	7	85*	54	47
V	1/2002 – 4/2007	LARC T4a	92**	35/65	0	55	34	11	-	-	95	71	58

* : Small bowel resections in 83% (122) of the patients are not registered as ETME/ multivisceral res.

** : 28 of the patients in Paper III are also included in Paper V.

Scattered tumour cells within the fibrosis, at or outside the mesorectal fascia were reported in Paper V with 55% TRG2-3 in pT4 tumours as well as in published abstract (Tanaka et al. 2008). These observations strengthen the need for surgical resection of all fibrosis in locations where MRI before treatment showed tumour to obtain optimal results. There has been a tendency over the last years to perform an increasing rate of low anterior resections (LAR's) in advanced rectal cancer (Crane et al. 2003a). The results show that fibrosis left *in situ* in advanced cases may contain

viable tumour cells, which may increase the late recurrences. In this way, the reported 28% local relapses after RT occurring more than 5 years after surgery could be explained (Coco et al. 2006). Thus a longer observation interval may be necessary to determine the true local recurrence rate after CRT. In Paper III the median interval to recurrence in the 23 patients who developed recurrence (12%) was 17 months, and two patients were diagnosed more than three years after surgery.

Complications

In Paper III, the LARC mortality within the first month was 2.5%. Non-lethal complications appeared in 41% of the patients. Deep abscesses or late perineal healing occurred in 25%, urinary tract infection in 17%, wound infection in 8% and pneumonia in 6%. Twenty-four urinary or bowel leaks (12%) made a resource demanding problem. Fifty-five re-operations were performed in 41 patients, most often because of bowel or urinary leaks, pelvic abscesses or bowel obstruction.

A 30-day postoperative mortality of 0.7% is no argument against LRRC surgery as in Paper IV, but the extent of the procedure is reflected in the number of major complications appearing in 46% of the patients. The complication frequency is also fairly high in other reports, varying from 15% to 60%. In our study we had to reoperate 27% of the patients. Although most authors report lower frequencies of reoperations it was nearly identical in the large study from the Mayo Clinic (Hahnloser et al. 2003).

Nearly all our patients in Paper II were in ASA group 2 and 3. Hessmann et al found high ASA score to be a predictor of perioperative mortality and long-time survival in unselected colorectal cancer populations but their mortality rate was three times higher than ours (Hessman et al. 1997). Other reports identify age (Edna and Bjerkeset 1998; Martijn et al. 2003) and ASA group (Edna and Bjerkeset 1998) as independent factors for postoperative death. We found ASA-scores 3 and 4 to be a predictor of urinary tract infections. Most of the studies on colorectal or rectal cancer suggest that surgery in the elderly is associated with significantly higher perioperative mortality than in younger patients. It is difficult to compare materials different in age, degree of elective surgery and extent of surgery performed. Perioperative mortality in ordinary electively operated patients vary from 1% to 12% (2000; Wiig et al. 2005a), rising to 5-23% in reports where both planned and emergency operations are included (Colorectal Cancer Collaborative Group 2000; Akoh et al. 1994; Damhuis et al. 1997; Edna and Bjerkeset 1998; Kingston et al. 1995). Damhuis found the mortality rate in unselected colorectal cancer patients to be 3% postoperatively in age 70-79 with a marked increase to 10% in patients aged 80 and over (Damhuis et al. 1997).

Our morbidity rate of 44% was within the previously published range (34%-43%) for elective major rectal cancer without multimodal treatment (Hessman et al. 1997; Longo et al. 1998; Puig-La, Jr. et al. 2000).

Multimodal treatment in the elderly

In Paper II we assessed the efficacy of multimodal therapy for LARC and LRRC in patients older than age 75 years. Cancer treatment varies considerably with age, and the proportion of patients treated with curative intent is reduced with increasing age (Arveux et al. 1997). The elderly over 75 years of age amount to 15% - 37% of rectal cancer patients in different reports (Damhuis et al. 1996; Kingston et al. 1995; Puig-La, Jr. et al. 2000) partly due to increased selection of cases with rising age and fewer old patients being referred to specialists for evaluation (Newcomb and Carbone 1993). The view that the general health condition of the patient is more important than age seems to gain an increasing degree of acceptance and we firmly believe that the three points formulated by Balducci should be focused upon (Balducci 2000): 1) Will the patient die of the cancer or with it? 2) Can the patient tolerate surgery and probable surgical complications? 3) Will the patient suffer from complication of his cancer in the future? The importance of the biological age is focused by the Colorectal Research Unit in Basingstoke where they advocate a starring system based on performance of lifestyle (Farquharson et al. 2001).

The Norwegian Rectal Cancer Project has shown that 75% of rectal cancer patients in Norway are operated with major resections, either palliatively (11%) or with curative intent (64%) (Wibe et al. 2002a). We had curative intent in 84% of the elderly, suggesting more extensive selection and maybe also a more aggressive surgical approach in our hospital. Materials concerning rectal cancer of different ages tend to have higher proportions of localised disease in the elderly patients (Colorectal Cancer Collaborative Group 2000; Puig-La, Jr. et al. 2000; Violi et al. 1998). This was probably due to selection bias and it is conceivable that more elderly with advanced rectal cancer may have been managed non-operatively or with best supportive care (Puig-La, Jr. et al. 2000).

Despite a generally increased use of irradiation in the last decade, patients aged 75 years or older have been less likely to receive RT (Barrier et al. 2003; Endreseth et al. 2006; Violi et al. 1998). Both high age (Violi et al. 1998), indication for irradiation and a high proportion of recurrent cancers (Wiig et al. 2005b) tend to reduce the proportion of sphincter preserving procedures in primary and non-advanced rectal cancers. On the other hand, in Basingstoke, of non-irradiated patients over 75 years of age given LAR, and in whom the defunctioning stoma was closed one year after surgery, only 15% had problems with bowel function (Phillips et al. 2004).

Life expectancy decreased with increasing age, independent of diagnosis. In Paper II 40% of males died during the first year postoperatively in contrast to 20% of females. In these estimates patients with known distant metastases at the time of surgery (M1 stage) were included. However, the 30-day mortality rate in Paper II was low. In the Dutch CCC South and West combined dataset several confounding factors, such as treatment-related complications and comorbidity was thought to be responsible for a high 6-month postoperative mortality rate in elderly (Rutten et al. 2008). After the first year postoperatively, the rates decreased and were nearly the same as in age- and gender matched groups. A large proportion of patients in all elderly subgroups will survive for two or more years after surgery (2000; Violi et al. 1998).

If advanced tumours were not removed surgically, the patients might develop secondary abscesses or fistulas to the bladder, vagina or small bowel, experience complicated pain problems due to tumour infiltration into nerves or obstruction of the bowel. In absence of advanced metastatic disease or significant medical contraindications to surgery, we therefore put a lot of effort into achieving local tumour control. Elderly ought to be considered for rectal cancer surgery, even after prolonged preoperative RT and they should be evaluated by multidisciplinary teams in specialized institutions.

In Paper II, 10 of the 35 patients with LRRC were 80 – 84 years of age at time of operation. They lived median 23 months after surgery (range 17-90) and half of them obtained an R0 resection.

MRI in stage T4a LARC

MRI is considered the best method for examination of LARC and for predicting the CRM status, depth of extramural tumour and nodal status (Beets-Tan et al. 2005;MERCURY Study Group 2006;MERCURY Study Group 2007). Few prospective studies or retrospective audits have focused on MRI and histopathology in rectal cancer surgery, irrespective of tumour stage (Beets-Tan et al. 2005;Kuo et al. 2005;Kuo et al. 2007;Maretto et al. 2007;MERCURY Study Group 2006;MERCURY Study Group 2007;Videhult et al. 2007). MRI in LARC before neo-adjuvant treatment compared to the removed specimen has been the focus of some reports (Chau et al. 2006;Kuo et al. 2005;Rao et al. 2007) usually containing a very small proportion of mrT4 tumours (Allen et al. 2007;Blomqvist et al. 2002;Chen et al. 2005;Kulkarni et al. 2008;Maretto et al. 2007;Torkzad et al. 2007). No study, to our knowledge, has tried to evaluate the clinical importance of the preoperative MRI after neo-adjuvant treatment or TRG data from a relatively large number of MRI diagnosed T4 tumours.

We found 10% T-downstaging evaluated by cMRI and yMRI, compared to 17% observed by Allen in a small study on 30 patients including only nine cmrT4 patients (Allen et al. 2007). In contrast, in our study the total accuracy of yMRI was only 40%, overstaging 59%, compared to histopathological staging.

Due to the problem of detecting islets of viable tumour within fibrosis or mucin deposits, our radiologists have interpreted the fibrosis/ mucin as possibly containing tumour cells leading to a low proportion of T-downstaging. However, our results with a total downstaging in T4a level from cMRI to final pathology of 64% is similar to reports from a small series of 22 and 18 T4 tumours (73%-76%) (Chau et al. 2006;Kuo et al. 2007).

yMRI downstaging could be observed even when the primary tumour was not decreased in size or stage. Our results confirm the ability of neo-adjuvant treatment to give a mrN-downstaging in two-thirds of LARC patients as previously reported in

smaller series (Allen et al. 2007;Kuo et al. 2005). It should not be forgotten, however, that the accuracy of MRI compared to final pathology is only 50% with one-third of patients being overstaged by MRI. Understaging could be explained if pathological lymph nodes were not removed surgically or not detected by the pathologist.

Our radiologists have interpreted the fibrotic scar as possibly containing tumour, presuming that small islets of tumour cells would not make any visible difference to the MRI-signal. Within a voxel (the smallest imaging element), the dominating tissue will determine the signal. According to the dominance of fibrosis in TRG2-3, the yMRI signal from scattered tumour cells within fibrosis will be that of fibrosis. The signal from tumour cells will not be enough to alter the signal of the whole voxel, in contrast to the situation before treatment where tumour cells are usually densely organised and not scattered. Hence cMRI will more accurately demonstrate the presence of tumour. If tumour cells and fibrosis were more separated, as in TRG4-5, the signals might be discriminated and therefore TRG4-5 is more obvious due to less fibrosis.

We would expect that all 83 ymrT4 cases could result in a local recurrence if only a TME had been performed. However, 51 of these cases had a histopathological stage less than ypT4 and therefore no verified tumour outside the mesorectal fascia could be detected even though the yMRI suggested its presence. Thirty-nine of them had TRG1-3 and could be very difficult to classify histopathologically due to few tumour cells within an area mainly containing fibrotic tissue.

The histopathological complete response rate's (ypT0) after neo-adjuvant CRT vary with the type of chemotherapy added to the RT, the selection of patients, the proportion of T-stages and also with the irradiation regimen (Minsky et al. 1997;Onaitis et al. 2001;Vauthey et al. 1999). We found 10% histologically proven complete response in our study of only T4a tumours. The proportion may be increased by addition of induction chemotherapy with new drugs (Chau et al. 2006;O'Neill et al. 2007).

We presume that a MRI assisted technique for the pathological investigation of the areas at risk in an optimal histopathological slide can be of great value in discovering small nests of tumour tissue outside the mesorectal fascia (Figure 1 in Paper V, Figure 2). This could be important for future staging and planning of treatment. We will later address the results with this new technique from an ongoing study.

The area of failure after intentional curative resection was the pelvic wall in seven of our ten R1 resections with M0 disease. In six of seven cases we had signs of threatened margins on MRI both before and after neo-adjuvant treatment and in five of seven after neo-adjuvant treatment. Five of the seven patients had yMRI classified pathological lymph nodes on the pelvic wall. Among the ten failures, there were only two women. This might be due to the wide female pelvis and to the protective barrier effect of the vagina and uterus. We have earlier reported that women are less likely to have bladder involvement, only seen after previous hysterectomies (Larsen et al. 2008).

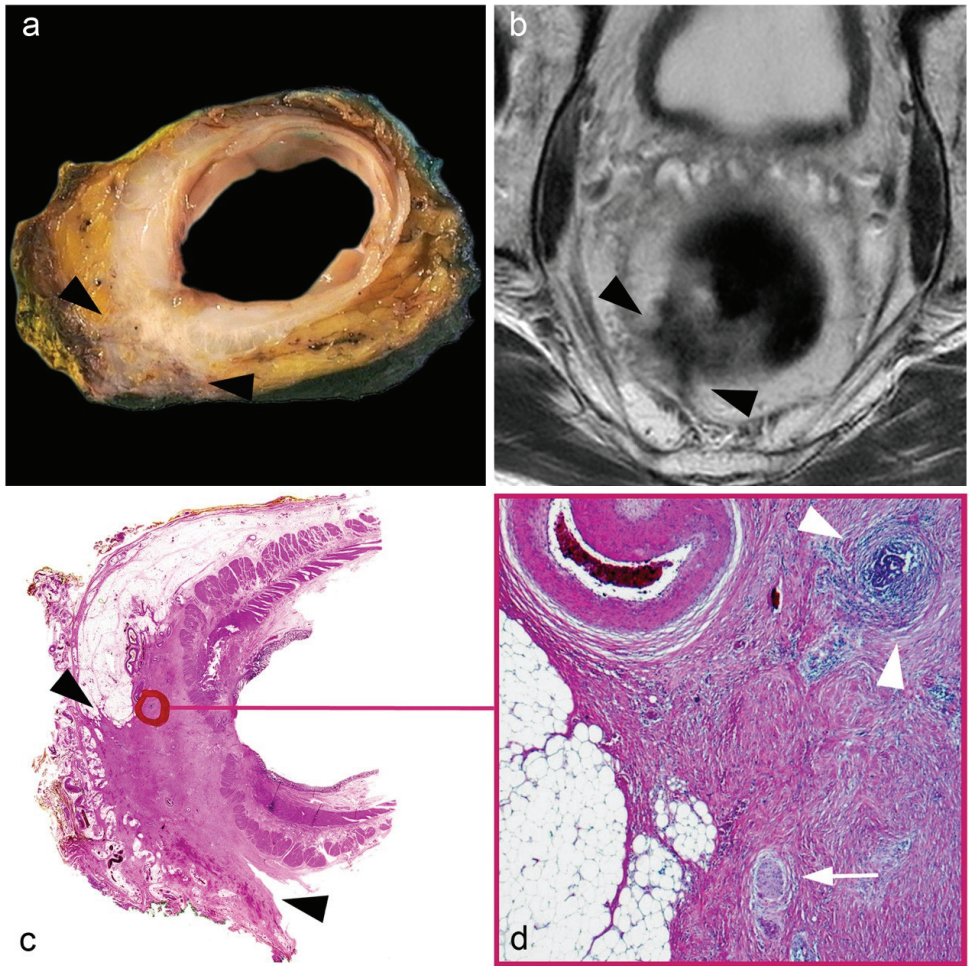


Figure 2.

Pathological investigation of the areas at risk after CRT (MRI assisted).

Tumour islet within fibrosis (black arrowheads) located in the pelvic side wall. (a) Resection specimen slice. (b) Corresponding transversal T2-weighted MRI obtained after radiation therapy. (c) Corresponding whole-mount histology (haematoxyline and eosine stained). Islet of tumour in red circle. (d) Original magnification x 25 of tumour nests (white arrowhead). Nerve originated from the pelvis side wall that is present close to the residual tumour (white arrow).

7. CONCLUSIONS AND FUTURE PERSPECTIVES

Radiological assessment with MRI of the pelvis identifies patients in need of neo-adjuvant treatment in both LARC and LRRc. A multi-disciplinary approach is important in reducing local recurrences by providing optimal preoperative staging, neo-adjuvant therapy and careful planning of surgery in specialized institutions.

Surgery in advanced tumours outside the mesorectal fascia should be handled with extended TME resections, mainly as *en bloc* resections. Surgery may be an option also in patients with local recurrence presenting with hydronephrosis.

A substantial number can become microscopically free of cancer with a high 5-year survival rate. Even patients with microscopic cancer remnant can benefit from such treatment, but not those with macroscopic cancer left behind. Multimodality treatment cures about half of the patients with M0 rectal cancer and loco regional control is acceptable. In addition, surgery often is the best palliation, even in the elderly.

MRI after neo-adjuvant treatment did not predict downstaging satisfactorily and in patients with histopathologically proven T4, fibrosis with scattered tumour cells remained in the 55% of patients with TRG2-3. Therefore, surgery should be performed in accordance with the pretreatment MRI to avoid late recurrences as a result of scattered tumour cells that might be left *in situ* within the fibrosis. Post treatment MRI is a poor predictor of final histology and should not be relied upon to guide the extent of surgical resection. However, the second MRI can be important for discovering disease progression in the few patients with progressive disease on RT/CRT, and can demonstrate tumour reduction to neo-adjuvant treatment.

In the future, more effective CRT protocols may reduce the need for ETME operation due to increased downstaging of tumour. The study has initiated a new approach to histopathological classification of the removed specimen where we introduce a MRI assisted technique for investigating the areas at risk outside the mesorectal fascia in the specimen.

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